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Crohn's disease in a defined population Results of surgical treatment



TOMAS LINDHAGEN

Malmö 1982



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CROHN'S DISEASE IN A DEFINED POPULATION
RESULTS OF SURGICAL TREATMENT

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av

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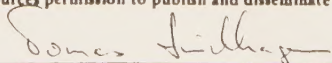
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Abstract In an analysis of a total, unselected series, consisting of all 207 patients, residents in the city of Malmö, Sweden, diagnosed as having Crohn's disease during the years 1958 through 1974, it was found that 52% of the patients, who underwent primary resectional surgery (95/182 patients), had the disease predominantly confined to the large bowel. In another 12 patients the disease was confined to the appendix. The median time between diagnosis and operation in 133 patients with preoperatively established diagnosis was short, four months for patients with predominantly small bowel disease, and eight months for those with predominantly large bowel disease. The frequencies of preoperative and early postoperative complications were low for these comparatively early operated patients. The early postoperative mortality rate was 1%. The recurrence rate after a median follow-up time of 9.3 years was 49% when calculated from crude figures (83/168 "radically" operated patients). The cumulative recurrence rate, calculated according to the actuarial method, was 53% at 15 years. The recurrence rate was not influenced by age, sex, duration of the preoperative disease history, extent of the lesions in the bowel or type of operative procedure. However, the recurrence rate for patients with major microscopical lesions in the resection margins was significantly higher than the rates for those without lesions or with minor lesions in the resection lines. Colectomy and ileorectal anastomosis was successful in 2/3 of the patients with apparently normal rectum at the time of operation. Rectal lesions did not disappear after diversionary surgery. An early postoperative small bowel radiography with normal findings indicated a low risk of recurrence.			
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RESULTS OF SURGICAL TREATMENT

TOMAS LINDHAGEN

MALMÖ 1982



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C. Lindström and A. Wenckert.

Recurrence Rate After Surgical Treatment for Crohn's
Disease.

Submitted Scand J Gastroenterol

- II. T. Lindhagen, G. Ekelund, L. Leandoer, J. Hildell,
C. Lindström and A. Wenckert.

Early Surgery for Crohn's Disease.

Submitted Scand J Gastroenterol

- III. T. Lindhagen, G. Ekelund, L. Leandoer, J. Hildell,
C. Lindström and A. Wenckert.

Crohn's Disease in a Defined Population.

Course and results of surgical treatment.

Part I: Small bowel disease.

Submitted Acta Chir Scand

- IV. T. Lindhagen, G. Ekelund, L. Leandoer, J. Hildell,
C. Lindström and A. Wenckert.

Crohn's Disease in a Defined Population.

Course and results of surgical treatment.

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The articles are referred to in the text by their Roman
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ABBREVIATIONS

SBD - Crohn's disease predominantly or exclusively confined to the small bowel.

LBD - Crohn's disease predominantly or exclusively confined to the large bowel.

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INTRODUCTION

Within the spectrum of intestinal disorders, non-specific inflammatory bowel disease - ulcerative colitis and Crohn's disease - represent challenging entities, since the etiology is unknown and the clinical course of the disease varies widely. Therefore, the treatment of patients, suffering from these illnesses, is a matter of continuous dispute.

Crohn's disease is a chronic inflammation of the bowel. During the course of the disease various local and systemic complications may occur, and sometimes these complications may become serious. Opinions differ how to treat this disease. Some authors claim, that surgery should be reserved as an ultimate resort of therapy (1, 2, 3, 4, 5), while others advocate a more aggressive approach towards surgical intervention (6, 7, 8, 9, 10). There are also great variations between reported results of therapy. For example, the recurrence rates, reported in the literature, range between 3% and 100% (11,12).

The present study focuses on the frequency of different pre- and postoperatively occurring complications in a series of unselected patients, in whom the treatment has predominantly been surgical, and comparatively early surgery has been performed. In addition, the recurrence rates after "radical" resection will be calculated, and some factors which possibly may influence the recurrence rate will be discussed.

HISTORICAL REMARKS

In the original report in 1932, Crohn, Ginzburg and Oppenheimer (13) described 14 cases suffering from a new disease involving the distal part of the ileum. They found a "sub-acute or chronic necrotizing and cicatrizing inflammation" with mucosal

ulcerations, mainly affecting young adults. The disease was called regional ileitis, since they did not find involvement of any other part of the bowel. Later on, however, it has become obvious that Crohn's disease may occur in any part of the alimentary tract.

There are, however, other reports apparently concerning the same disease published before the classical paper by Crohn et al (13). Combe in 1813 thus reported on a young man who for many years had complained of abdominal pain and subsequently died of intestinal obstruction (14). At the autopsy the distal ileum was found to be thickened and narrowed. A similar case was described by Abercrombie in 1828 (15). In the latter part of the 19th century Moore (1882) and Fenwick (1889) reported one case each (16,17). The young female, reported on by Fenwick, had stenosis of the bowel and fistulae.

In the beginning of the 20th century Lesniowski (1904) described one case, and Dalziel (1913) nine cases, of whom six were most likely to have Crohn's disease (18,19). Dalziel's description of the macroscopical appearance of the bowel - "an eel in a state of rigor mortis" - has often been quoted. These two latter reports never became widely recognized due to the facts that Lesniowski's report was written in Polish and that World War I broke out soon after Dalziel's report was published.

The original description in 1932 was soon followed by an increasing amount of reports. Involvement of other parts of the intestine was demonstrated by Harris et al in 1933 (jejunum), Colp in 1934 (colonic involvement), Barbour & Stokes in 1936 (duodenum), Ross in 1949 (stomach), Heffernon & Kepkay in 1954 (oesophagus) and Dudeney & Todd in 1969 (mouth) (20,21,22,23, 24,25).

In 1952, Wells described segmental granulomatous colitis, and Brooke in 1953 discussed the differentiation between ulcerative colitis and Crohn's disease of the colon (26,27). It was not until 1960, however, that the distinctions between these two entities were clarified by Lockhart-Mummery & Morson (28).

A most important report was published in 1954 by van Patter et al at the Mayo Clinic (1). This study concerned the outcome of medical and surgical treatment of 600 patients. Since the recurrence rate after surgery was found to be unacceptably high (62%), the prevailing therapy became more conservative during the following ten years. Later on, however, there was in many medical centres a shift in the policy back to resectional surgery. A huge amount of reports concerning the outcome of operative therapy has been published during the last two decades, but it has often been difficult to compare the results. For example, the recurrence rates reported have differed widely, due to the facts that some patient-series have been selected, or that there have been differences in follow-up time. In 1966, the statistician Hill described the actuarial method, which takes different lengths of the follow-up times into consideration (29). Lennard-Jones & Stalder in 1967 were the first clinicians to use this method, when calculating the recurrence rates (30). Later on, this statistical method has been used, for example, in the studies by de Dombal (1971), Greenstein et al (1975), Hellers (1979), Hellberg et al (1980) and Lock et al (1981) (31,32,33,34,35).

Important information about the mortality rate has been published by Truelove & Pena (1976) and by Prior et al from Birmingham (1981) (36,37). From the same city originates a long-term study of 174 patients, diagnosed before 1956 (Cooke et al, 1980) (38).

Most previous reports regarding surgical treatment have been

retrospective. However, Greenstein et al (1975) prospectively followed patients between 1969-1973 and Hellberg et al in 1980 reported on the recurrence rate in a prospective study from Göteborg (32,34). The above mentioned long-term follow-up study from Birmingham (Cooke et al, 1980) was also prospective (38).

Considering medicament treatment, many prospective studies have been published. In 1970, the US National Cooperative Crohn's Disease Study (NCCDS) was initiated. This important prospective, multicenter investigation mainly dealt with the effects of medicament treatment and was published in 1979 (39). This year also the first results of a prospective multinational survey on inflammatory bowel disease - the Organisation Mondiale de Gastroenterologie (O.M.G.E.) Survey was published (40). Another prospective study on the effect of an immunosuppressive drug, azathioprine (Imurel^R) was reported on in 1980 by Present et al (41).

The first Swedish report on Crohn's disease was published by Strömbeck in 1937 (42). Later on, many Swedish studies have been published. Microbiological and immunological investigations were performed by Persson (1974), Ahlberg et al (1978) and Krook et al (1981) (43,44,45). Increased incidence of Crohn's disease was reported by Brahme et al (1975), Bergman & Krause (1975) and HELLERS (1979) (33, 46, 47). Studies on metabolic and nutritional consequences of surgery in patients with Crohn's disease were performed in Göteborg by Filipsson et al (1978) (48). The effect of conservative treatment with metronidazole and sulphasalazine was reported by Ursing & Kamme (1975), Krook et al (1981) and Ursing et al (1982) (49,50,51).

Studies concerning the outcome of surgical treatment have been published from Uppsala (Krause et al, 1971; Bergman et al,

1977; Krause, 1978), Örebro (Wallensten, 1971), Stockholm (Hellers, 1979), Göteborg (Hellberg et al, 1980; Fasth et al, 1980) and Malmö (Wenckert, 1970) (8,9,33,34,52,53,54,55). In Linköping, Heuman et al (1980) studied some aspects on intestinal and extraintestinal abnormalities in patients with Crohn's disease (56,57).

ETIOLOGY

The etiological and pathogenetic mechanisms of Crohn's disease still are completely unknown. Many attempts to find a causative agent have been made. Dalziel (1913) suspected *Mycobacterium pseudotuberculosis*, but this organism has not been isolated from patients with Crohn's disease (19). Mitchell & Rees in 1970 tried to find a transmittable agent by injecting homogenates from Crohn-tissue into mice's footpads (58), and this study was soon followed by others on the same idea. No convincing evidence for a transmittable organism, neither bacteria, nor virus, has, however, yet been published. Other subjects which have been discussed are immunological, dietary and vascular factors (for review, see Sachar et al, 1980) (59).

EPIDEMIOLOGY

From available reports on the incidence of Crohn's disease it is obvious that this condition is encountered most frequently in the western area, but practically unknown in Africa and Asia. Until the beginning of the sixties the incidence was low also in western countries (Evans & Acheson, 1965; Gjone et al, 1966; Norlén et al, 1970) (60,61,62), but then the incidence gradually increased, as shown by Kyle (1972), Bergman & Krause (1975), Brahme et al (1975), Mayberry et al (1979), Hellers (1979) and Sedlack et al (1980) (33,46,47,63,64,65). In some

countries, however, the incidence remained low (Basle area, Fahrländer & Berlocker, 1971; Copenhagen, Høj et al, 1973; Northern Ireland, Humphreys & Parks, 1975) (66,67,68).

The only studies on the incidence of Crohn's disease in a defined population came from Aberdeen (Kyle, 1971), Malmö (Brahme et al, 1975), Stockholm (Hellers, 1979) and Cardiff (Mayberry et al, 1979) (33,46,63,64). The annual incidence of Crohn's disease in the three latter cities were, in the beginning of the seventies, about 5/100 000. The age specific incidence showed a marked peak during the third decade.

Reported prevalence figures for the disease range between 17 and 106 per 100 000 (Rozen, 1979; Sedlack et al, 1980) (65,69).

As reported by Hellers in 1979, the incidence rate reached a plateau during the seventies (33). He suggested that the population had reached its maximum susceptibility to the disease. Mayberry in 1982, however, reported that the incidence continued to rise suggesting that the plateau is not yet stable (70).

CLINICAL ASPECTS

The main subjective symptoms of the disease are diarrhoea, abdominal pain and general malaise. The onset is, in many cases, insidious. In some patients, however, the onset may be acute, mimicking appendicitis. Intestinal obstruction may appear as an early or even first indication of the disease. In some cases various systemic disorders, such as erythema nodosum and arthritis, may precede the intestinal manifestations.

Objective signs are weight loss and steatorrhea, the latter pattern almost invariably present in cases with involvement of the distal ileum. Various nutritional defects develop, for example anemia, decrease in serum albumin due to increased excretion from the diseased bowel wall and, in patients with a long history, deficiency of vitamin B₁₂ due to impaired absorption from the involved terminal ileum. Some patients with long-standing disease of the distal part of the small intestine develop biliary stones, probably due to impaired entero-hepatic circulation of bile acids. The frequencies of urinary stones and peptic ulcerations are also reported to be increased in patients with Crohn's disease.

One of the hallmarks of Crohn's disease is the propensity for fistula and abscess formation. These fistulae/abscesses develop due to the formation of deep inflammatory fissures, penetrating through all wall-layer. These types of complications are usually seen in patients with relatively long disease history. There are three main types of fistulae: *a/ entero-cutaneous fistulae*, often occurring after explorative laparotomy or appendicectomy, *b/ internal fistulae*, extending into the mesentery or to adjacent loops of the intestine or to other neighbouring structures, and *c/ anal fistulae*. The latter type of fistulae may in some cases constitute a prodrome, preceding the onset of the intestinal symptoms, and are even seen in cases without other involvement of the rectum.

The clinical course often runs with periods of exacerbation, followed by quiescent disease, but in a few percentage of the cases with colonic involvement, the exacerbation may end up in a life-threatening fulminant stage with toxic megacolon.

Objective signs of an active disease are, for example, elevation of ESR, increased serum orosomucoid concentration,

decreased total iron binding capacity and fever.

Occasionally the disease undergoes spontaneous regression.

DIAGNOSIS

In most cases the diagnosis of Crohn's disease is based on typical clinical signs, supported by radiography of the intestine, biopsy, blood chemistry and, in cases operated upon, by the macroscopical appearance at laparotomy and histopathological examination of resected specimens.

Radiography constitutes the most valuable method to diagnose the disease. The common methods used are the follow-through technique when examining the small bowel, and the conventional barium contrast enema when the large bowel is examined. Other techniques, however, have been developed, the duodenal intubation method described by Sellink (1971) and the double contrast barium enema technique described by Welin (1962) (71,72). These two latter methods make it possible to identify the earlier manifestations of the disease, the small "aphthoid" ulcers of the mucosa (fig 3 and 4).

Endoscopic examinations of the bowel, including biopsy, are also important for diagnosis. Several biopsies should be taken in order to facilitate the histopathological evaluation, since the inflammation is often focal (73).

The macroscopical appearances of small bowel Crohn's disease are typical (fig 1). The intestine is thickened, oedematous and rigid, with single or multiple strictures. In advanced cases the oedematous mesenterial fat almost entirely surrounds the bowel. Lymph nodes in the regional mesentery are often enlarged. When the bowel is opened, the mucosa in the most

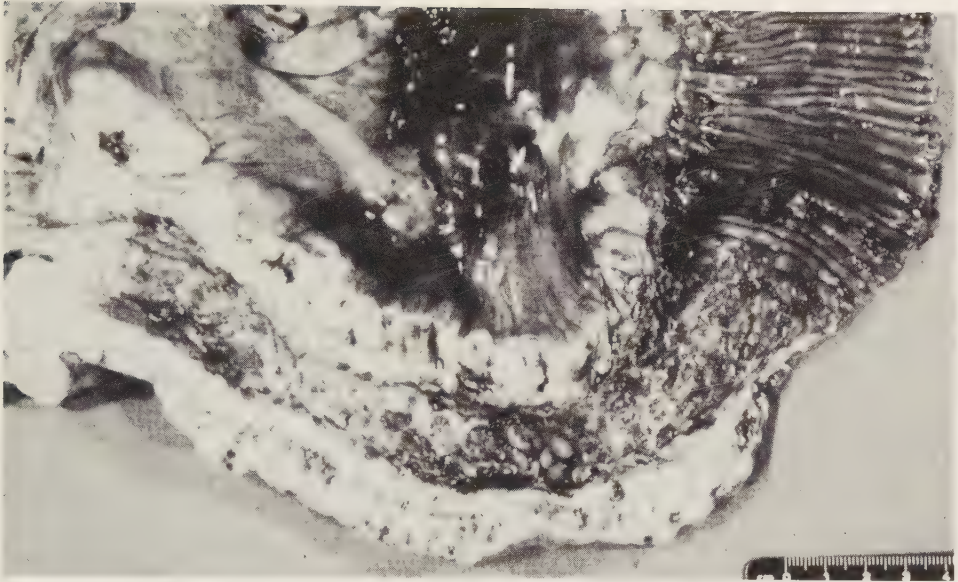


Fig 1: Crohn's disease predominantly confined to the distal ileum (SBD).

involved part of the gut, usually the distal part of the ileum, is found to be ulcerated. The ulcers are often discontinuous. Sometimes the mucosa has a "cobble-stone"-like appearance. This appearance is due to fissures and ulcers, surrounding islands of mucosal remnants which are raised by the underlying oedema. Proximally the ulcerations and oedema gradually disappear and in these less involved parts of the intestine the above mentioned "aphthoid" ulcers are often seen, diffusively scattered in the mucosal layer.

The gross appearance of the large bowel may resemble those of Crohn's disease of the small intestine, i.e. thickening of the bowel wall and "cobble-stones"-like mucosa (fig 2). The disease may involve either the right colon, the whole colon with or without concomitant lesions in the rectum or

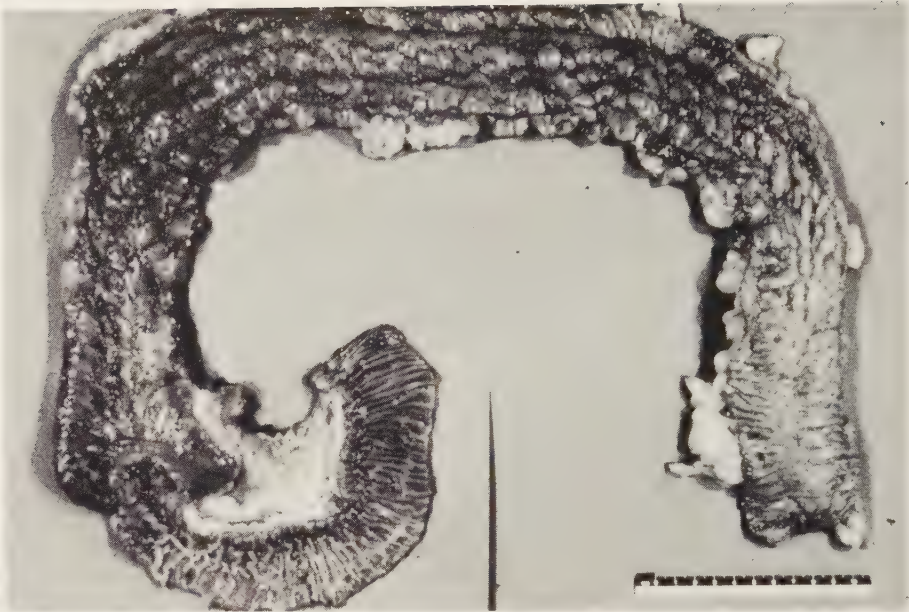


Fig 2: Crohn's disease predominantly confined to the large bowel (LBD).

may appear as "skip lesions" with macroscopically uninvolved segments in between. Strictures and fistula formation may also occur, though less frequently than in the small gut. Sometimes, however, the changes can be less characteristic and be difficult to distinguish from those in ulcerative colitis. This is especially true in cases with fulminant colitis.

At microscopy, the most reliable diagnostic feature is the demonstration of sarcoid-like granulomas with giant cells of the Langhan type (fig 5). If these granulomas are absent, there are other typical histopathological features which give diagnostic information. These are the above mentioned focal inflammation and transmural inflammation, creating fissures or sinuses. Lymphoid aggregates, fibrosis and crypt abscesses

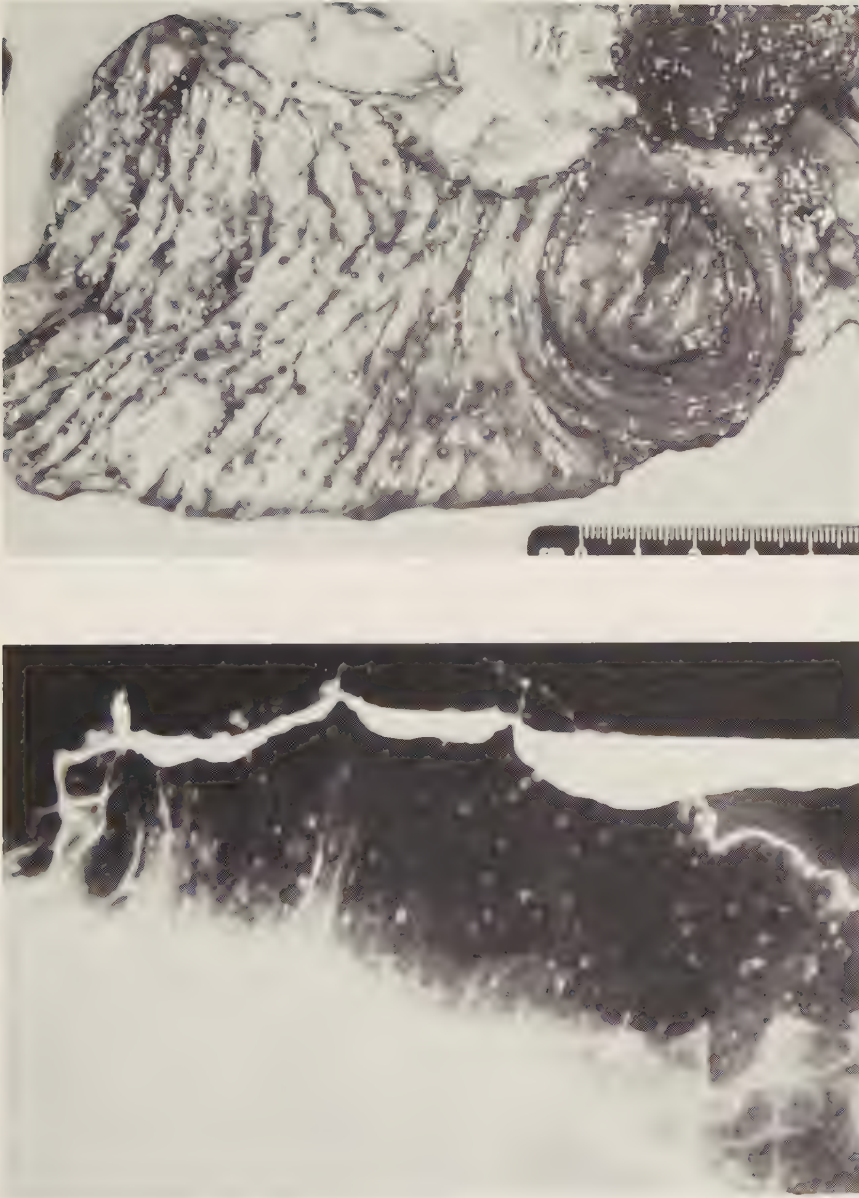


Fig 3 and 4: Early "aphthoid" ulcers in Crohn's disease of the large bowel, as seen on radiograms, performed with the double contrast enema technique (left), and in an opened operative specimen (right).

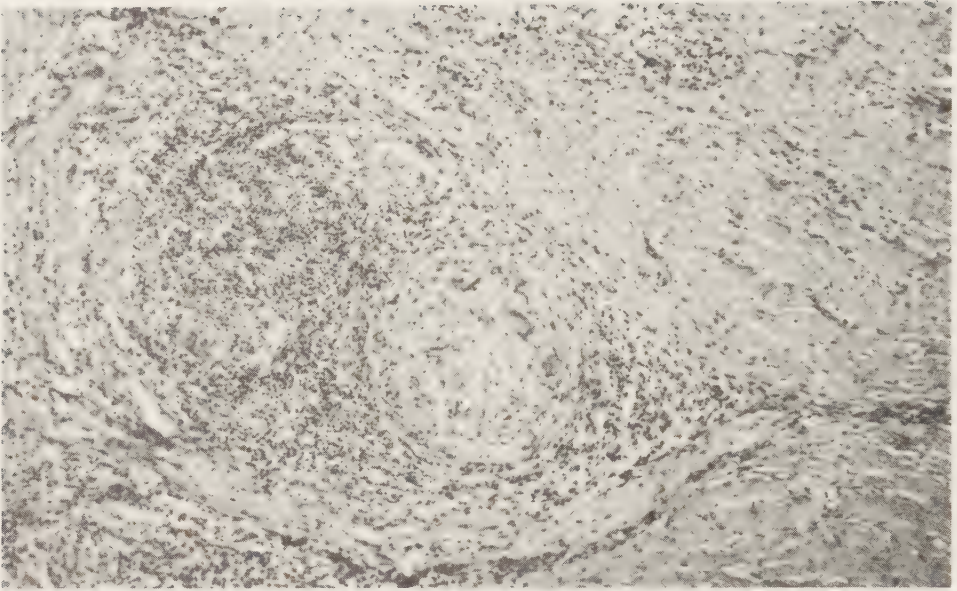


Fig 5: Histological section of an operative specimen, showing a non-caseating granuloma with giant cells of the Langhans type (Htx - eos x 120).

are other characteristics of the disease, the latter feature, however, not as frequently seen as in ulcerative colitis.

The ulcers are often situated on lymphoid follicles, and the initial "aphthoid" ulcers are supposed to originate from these lymphatic aggregates. Another important diagnostic feature is the preservation of the goblet cells in the mucosa.

DIFFERENTIAL DIAGNOSIS

There are other diseases, which may resemble Crohn's disease. Earlier, probably many cases affecting the small bowel were diagnosed as having tuberculosis, which is distinguished by extensive caseating of the granulomas and the demonstration

of acid-fast bacilli.

Sometimes, at laparotomy, in case of a presumed appendicitis, the terminal ileum may be found swollen and reddened, but the encroachment of the mesentery on the bowel wall, a typical finding in Crohn's disease, may be missing. This type of acute ileitis may be due to a *Yersinia enterocolitica* or *Yersinia pseudotuberculosis* infection, as established by postoperative bacteriological cultures and serological tests. This form of ileitis heals spontaneously and resection of the bowel should not be performed.

A distinction between Crohn's colitis and ulcerative colitis can be achieved in most cases. Internal fistula and abscess formations are often seen in patients with Crohn's disease but less common in patients with ulcerative colitis. If the rectum is uninvolved, the patient is likely to suffer from Crohn's disease. Intestinal bleeding is said to be less frequent in Crohn's disease than in ulcerative colitis, while the frequencies of systemic complications, such as arthritis or erythema nodosum, are equal for both diseases. The inflammation of the mucosa in patients with Crohn's disease is often focal, contrary to the diffuse appearance of the inflammation in ulcerative colitis, as seen at histopathological examination.

In some cases, however, a true distinction between the two entities can not be established. These patients often have a short disease history and most of them are operated upon as emergency cases, due to fulminant colitis. They generally constitute about ten percent of all cases with chronic inflammatory colitis, and are, in the absence of better designation, called "indeterminate colitis" (74,75). On clinical grounds one may suspect ulcerative colitis, due to the fact that most of the surviving patients have no further manifestations of the disease in the small gut. Histopathologically, however,

no certain diagnosis can be achieved.

Other differential diagnoses are ischemic colitis, pseudomembranous colitis and dysentery.

THERAPY

Since the etiology of Crohn's disease still is in obscurity, there is no causal treatment. The symptomatic treatment includes correction of nutritional defects, which develop due to insufficient food intake, reduced absorptive capacity of the bowel and loss of serum proteins into the lumen of the bowel. A low-fat, high-protein and high caloric diet should be maintained.

Medicamental therapy with corticosteroids, antibiotics and sulphasalazine (Salazopyrine^R) is widely used, especially in the treatment of active disease. As found in the U.S. National Cooperative Crohn's Disease Study (NCCDS, Summers et al, 1979), corticosteroids did better than placebo in the management of small bowel disease, whereas sulphasalazine did not (39). When treating active Crohn's colitis, the finding was quite the contrary. Neither corticosteroids nor sulphasalazine were shown to be of advantage, when quiescent disease was treated.

Recently, the use of immunosuppressive drugs, such as azathioprine (Imurel^R), or its active metabolite, 6-mercaptopurine, was reported to be effective in the management of Crohn's disease (Present et al, 1980) (41). In the NCCDS, however, no effect of these drugs was found (39). The study by Present et al and the NCCDS, however, are not completely comparable. In the former study, azathioprine was used in combination with corticosteroids or sulphasalazine, while in the NCCDS

azathioprine alone was tested. There were also differences in dosage between the two studies. According to Lennard-Jones (1981) and Singleton (1981) immunosuppressive therapy should be used only in selected cases due to dangerous side effects (76,77). Further randomized trials must be performed, before this controversy is solved.

In 1975, Ursing & Kamme reported that metronidazol was successful in the treatment of patients with Crohn's disease (49). The effect of this drug, however, has been impeached by others (Allan & Cooke, 1977) (78). In 1982, Ursing et al presented the results of a randomized, cross-over multicentre study (51). It was concluded that metronidazol was slightly more effective than sulphasalazine in the treatment of active Crohn's colitis.

Even if medicamental treatment with the above mentioned drugs may reduce the bowel inflammation for shorter periods, this therapy frequently fails in the long run, and most patients sooner or later are operated upon. Crohn et al in 1932 stated, that "the proper approach to a complete cure is by surgical resection of the diseased segment of the small intestine and of the ileo-caecal valve with its contiguous caecum" (13). Unfortunately, this form of treatment has been found to be far from satisfactory, if measured by means of the high recurrence rate after operation. This is also the main reason why many physicians are reluctant to surgery, and continue to treat the patients conservatively. According to some authors, surgery should only be carried out as an ultimate treatment (1, 2, 3, 4, 5). Others advocate a more aggressive approach, pleading for earlier surgery in order to avoid dangerous complications and serious nutritional disturbances (6, 7, 8, 9, 10). The surgical procedures employed are more or less "radical" resections of the bowel, by-pass procedures with or without exclusion of the diseased bowel segments and resection together with different kinds of entero-

stomas.

By-pass procedures are, especially in North America, preferred by many surgeons, but the recurrence - or relapse - rate after this type of operation is higher than after resectional surgery (79) which is the procedure most commonly used in Europe. Resection of the bowel, however, may be more or less "radical". Some authors prefer limited resections, being of the opinion that the patient may develop serious metabolic disturbances, if too much of the bowel is resected. Krause et al in 1971 stated, that right hemicolectomy rather than ileocecal resection should be carried out in patients with ileocecal involvement, since the recurrence rate was lower after this procedure than after ileocecal resection (52). However, since the recurrence in most cases occur on the proximal side of the anastomosis, Fasth et al in 1980 advocated a limited resection of the right colon in these cases (80).

INTRODUCTION TO THE PRESENT INVESTIGATION

During the fifties and the first few years of the sixties, the number of patients in Malmö, suffering from Crohn's disease, was small, but as the incidence rose (Brahme et al, 1975) (46) the experience in treatment of this disease increased. Due to some serious preoperative complications, there was a gradual shift in the attitude towards earlier surgical intervention, and this attitude was prevailing during the latter part of the investigation period.

During this period some questions arose concerning the surgical treatment of patients with Crohn's disease. Firstly, could earlier performed surgery reduce the recurrence rate? Secondly, could the morbidity be decreased with earlier surgical intervention? Thirdly, could the mortality rate be diminished, and fourthly, was there any sense in sparing the

rectum in cases with colonic involvement? Results concerning the first part of the investigation period have previously been published (Wenckert et al, 1970) (55).

In 1977, a group consisting of surgeons, one radiologist and one pathologist set about with a thorough scrutinization of all cases. This could be performed since all case records, radiographical films and histological sections from biopsies and specimens had been kept. Since 1969, all specimens themselves have been kept and it was thus possible to take new histological sections. At this reexamination all patients could be reevaluated and the results are given in the present thesis.

AIMS OF THE STUDY

The present material consists of a consecutive series of unselected patients in the defined population of Malmö. The purposes were to study:

- 1 The frequency of various sublocalizations of the disease in the total series.
- 2 How the diagnosis was achieved preoperatively, and how the extent of the disease, as assessed at preoperative radiography, correlated to that found at the time of operation and the reevaluation performed.
- 3 The frequency and severity of preoperatively developing local and systemic complications, in relation to the length of the disease history.
- 4 The frequency and severity of early and late postoperative complications, especially in patients with preoperatively established diagnosis of Crohn's disease.

- 5 The recurrence rate after "radical" resectional surgery in relation to different factors, such as sex, age, duration of the preoperative disease history, extent of the lesions in the bowel, surgical procedures performed and the histopathological appearance of the resection margins.
- 6 The risk of having a second resection for recurrence.
- 7 The fate of the rectum.
- 8 The clinical course and outcome of treatment, especially in surgically treated patients.

MATERIAL AND METHODS

PATIENTS

Included in the study are all residents in the city of Malmö, Sweden, who during the years 1958 through 1974 were diagnosed as having Crohn's disease. The patients were traced in the way reported on by Brahme et al (1975) in an epidemiological survey, covering the years from 1958 through 1973 (46). The patients, diagnosed during 1974 were traced mainly in the same way.

There were altogether 207 patients. During the period, 194 of the patients were operated upon. In 170 of these 194 patients a primary "radical" resection (see definitions) was performed, while in 12 patients only part of the most heavily involved bowel was resected. In another 12 of the patients operated upon, the disease was confined to the appendix vermiformis. Three of the remaining 13 patients, diagnosed but not operated upon during the period of investigation, were subjected to a primary operation during the follow-up period.

There were 93 males and 114 females. The age at the time of the primary operation for the 182 patients, who underwent resection of the bowel, ranged between 10 and 79 years (median 24 years, mean 28.4 years) (III, IV). The majority of the patients ($116/182 = 64\%$) were between 16 and 30 years of age.

The corresponding figures for the 12 patients with Crohn's disease confined to the appendix were: range 9 - 42 years, median 22 years, mean 21.5 years (V).

The age at the time of diagnosis for the remaining 13 patients not operated upon, ranged between 17 and 43 years (median 27 years, mean 29.7 years). Seven of these patients were between 16 and 30 years of age.

SURGICAL POLICY

During the operation the policy was to resect all macroscopically involved intestinal tissue, together with related mesentery and involved lymphatic nodes, if possible. However, in cases with rectal involvement, the rectum was often left. The specimens were peroperatively opened for a naked-eye examination. If there were lesions near the resection margins, a further part of the bowel was resected and inspected. This policy was adhered to in practically all cases, except for those operated upon during the first few years of the investigation period.

Concerning the lymph nodes, the intention was to remove all macroscopically enlarged nodes in order to see if the recurrence rate thus could be diminished. Information in the records, however, whether all nodes had been removed or not, were missing in many cases (25%). Thus, unfortunately no conclusions could be drawn regarding the correlation between lymphatic node removal and recurrence risk.

HANDLING OF THE SPECIMENS

As a rule, the specimens after preparation were measured, macrophotographed and then fixed in 10% formalin solution on large, specially made trays. After fixation a large number of histological sections from the bowel and the lymph nodes were prepared and examined.

CRITERIA FOR RADIOLOGICAL AND HISTOPATHOLOGICAL DIAGNOSIS

At the reexamination and reevaluation performed, the radiological criteria of Crohn's disease used were in accordance with those described by Sellink (1971), Laufer (1975) and Hildell (1979) (71,81,82).

The histopathological criteria for diagnosis were in agreement with those reported by Lockhart-Mummery & Morson (1964) and Price & Morson (1975) (83,84). The diagnosis was supported by the findings of giant cell granulomas in resected specimens of the bowel in 84% of the 194 cases, operated upon.

FOLLOW-UP

All patients were postoperatively examined at Malmö General Hospital. The policy was to examine the patients clinically several times during the first postoperative year, and thereafter yearly, if possible. As a rule, at these check-ups body-weight and at least serum hemoglobin level and ESR was measured. In the later part of the study, more extensive blood chemistry analyses were performed. Sigmoidoscopy was performed in most patients. The policy was also to perform an early postoperative radiography of the bowel.

During the follow-up period, 26 of the 182 resected patients moved out from the city and were thereafter examined elsewhere. The results of these examinations were included in this analysis.

At the end of the follow-up period, December 31st 1979, the median time between the primary procedure and the latest clinical examination or the date of death for the 182 resected patients was 9.2 years (mean 10 years, range 9 months - 19.6 years) (III, IV).

Seven of the 12 patients with the disease confined to the appendix were postoperatively examined at Malmö General Hospital. The other five patients were asked by mail about their state of health after the operation. The median time between operation and the latest clinical check-up or the date of answer to the inquiry, was 13.8 years (mean 12.3 years, range 6.3 - 16.8 years) (V).

Two of the 13 patients, not operated upon during the investigation period, were lost to follow-up, three months and 2.3 years after diagnosis, respectively. The median follow-up time for the remaining 11 cases was 9.3 years (mean 10.9 years, range 6.9 - 20.7 years).

DEFINITIONS

1. Radical resection: all macroscopically involved intestine has been resected, except for any lesions in an excluded rectum, as assessed at the time of the operation.
2. Palliative operation: part of the involved intestinal tissue was resected, or the involved intestine by-passed or excluded.
3. Ileocolic resection: ileocecal resection or right hemicolectomy, or re-resections after such procedures.
4. Recurrence: The appearance of objective signs - defined radiologically, endoscopically or histopathologically - of Crohn's disease in the bowel of a patient who has pre-

viously had a resection of all macroscopically diseased tissue (the Cape Town Classification) (85).

5. Quality of life: As assessed at the reevaluation, the patients were divided into three groups, according to the degree of general health - "quality of life" - at the latest clinical check-up:

Quality of life I: the patient was in a good general state of health, able to do full time work and to have normal leisure time activities.

Quality of life II: the patient was able to work part time and the leisure time activities were restricted due to diarrhoea, pain etc.

Quality of life III: the patient could not work at all and the leisure time activities were severely restricted by for example frequent diarrhoea, general weakness or pain.

STATISTICS

Differences between crude recurrence rates were evaluated by means of Chi square tests. A p-value less than 0.05 was considered to indicate a significant difference.

When calculating the cumulative recurrence rates, the actuarial method or life table method described by Hill in 1966 and by Andersen & Bonnevie in 1971 was used (29,86). The data were analysed with a computer type Hewlett-Packard 9845b, giving estimated recurrence rates and the limits of the 95% confidence interval for each of the postoperative years.

RESULTS

I. PATIENTS SUBJECTED TO RESECTIONAL SURGERY

Resection of the bowel as the primary surgical procedure was performed in 182 patients. In order to facilitate the reading of the results, these patients are divided into two groups, according to the site of involvement in the bowel: SBD = patients with the lesions predominantly or exclusively confined to the small bowel. LBD = patients with the lesions predominantly or exclusively confined to the large bowel.

The patients were also divided into two groups, according to whether the diagnosis of Crohn's disease was preoperatively known or not: Group A consists of 133 patients, in whom the diagnosis was preoperatively established, while group B contains the remaining 49 patients.

Duration of the preoperative disease history

The time between subjective onset and the diagnosis, and between diagnosis and the primary operation for the 133 patients with preoperatively established diagnosis (group A), are seen in table I. As seen in the table, the median time between onset and diagnosis was equal for both groups of patients (SBD and LBD), while the median time between diagnosis and operation was twice as long for patients with LBD (II).

The length of the preoperative disease history for the 49 patients, supposed to suffer from other diseases, varied according to the site of the lesions in the gut. Fifteen patients, with LBD, were preoperatively erroneously diagnosed as having ulcerative colitis, and the median time between diagnosis and operation for these patients was 3.2 years (mean 5.5 years, range 1 month - 17 years) (IV).

Time interval	SBD (n=60)	LBD (n=73)
<u>Onset-diagnosis</u>		
Median	5 months	5 months
Mean	1.3 years	11 months
Range	1 month-12 years	0-5.8 years
<u>Diagnosis-operation</u>		
Median	4 months	8 months
Mean	1 year	1.5 years
Range	1 month-7.7 years	1 month-12 years
<u>Onset-operation</u>		
Median	1.3 years	1.8 years
Mean	2.3 years	1.9 years

Table I: Duration of the preoperative disease history
for 133 patients with preoperatively established
diagnosis of Crohn's disease.

The duration of the disease history for 19 of the remaining 34 patients was short, one month or less. Six patients had a history ranging between two and six months, while the remaining nine cases had a history between ten months and nine years. Most of these patients (21 cases) were operated upon due to suspicion of appendicitis or appendiceal abscess, or due to intestinal obstruction (II).

Preoperative diagnosis

In 24 patients the primary operation was performed as an emergency one, without preoperative radiography of the bowel. The number of radiological examinations for the remaining 158 patients are seen in table II.

	<u>SBD</u> (66 examined patients)	<u>LBD</u> (92 examined patients)
Small bowel examination	115	150
Large bowel examination	109	257
	224	407

Table II: Number of preoperatively performed radiological examinations in 158 patients with Crohn's disease

The diagnosis of Crohn's disease could radiologically be established in 60 of the 66 patients (91%) with SBD (III), and in 69 of 92 patients (75%) with LBD (IV). In 16 of these 129 patients, the disease was discovered at a previous appendectomy, before the major intestinal resection.

Erroneous radiological diagnoses in the remaining 29 patients were: ulcerative colitis (18 patients), malignancy (5), appendiceal abscess (2), irradiation injury (1) and polyposis coli (1). In two cases no firm diagnosis was achieved.

Three of the 18 patients, preoperatively radiographically diagnosed as having ulcerative colitis, were on clinical grounds believed to suffer from Crohn's disease (IV).

In the initial reports from the histopathological examination of the resected specimens, a certain diagnosis of Crohn's disease was assessed in all cases but seven. In five of these seven cases, the first diagnosis was ulcerative colitis, while the diagnoses in the remainder were "indeterminate colitis"

and "developmental defect", respectively. Later on, after re-examining the histological sections, the diagnoses were changed to Crohn's disease in all seven patients.

To elucidate the difficulties of achieving the firm diagnosis of Crohn's disease, all cases with so called "indeterminate colitis" were reexamined as well (IV). This group consisted of 12 patients, of whom ten were operated upon. The remaining two patients were conservatively treated. Both died, and autopsy was performed in both patients.

In all twelve patients, fulminant exacerbation of the colitis developed. Histopathologically, four cases had features that could suggest Crohn's disease, and in another two there were microscopical characteristics which might indicate ulcerative colitis. In the remaining six patients, no distinct diagnosis could be made.

Extent of the lesions at preoperative radiography

The site of involvement in the bowel, as assessed at preoperative radiography, differed in some cases from that, found at the time of operation and at the reexamination performed. The extents, as judged at the reevaluation, are seen in table III and IV.

The extent of the lesions in the terminal ileum, was in accordance with that found at operation in all cases but three (III, IV). The extent of the disease, proximal to the distal part of the small bowel, however, could not be assessed at radiography, due to low diagnostic accuracy of the radiographic methods used (III). In 20 cases, lesions in the right hemi-colon (4 patients) the left hemicolon (9), the entire colon (6) and the rectum (1) were overlooked at radiography (IV).

Extent	Number of patients %
Small bowel, limited	4
Distal ileum only	28
Distal ileum + cecum	47
Cecum only	3
Distal ileum + right colon	11
Distal ileum + colon except rectum	29
Distal ileum + colon including rectum	35
Colon only, except rectum	1
Colon only, including rectum	10
Sigmoid colon only	1
Rectum only	1
	170

Table III: Extent of the lesions at the time of primary "radical" operation, as assessed at the reexamination.

Extent	Number of patients
Small bowel	5
Small bowel + right colon	3
Small bowel + colon including rectum	3
Duodenum + small bowel + colon including rectum	1
	12

Table IV: Extent of the lesions at the time of primary palliative operation, as assessed at the reexamination.

As a consequence of this overlooking of lesions in the large bowel, ileocolic resection and anastomosis between a small bowel with microscopically diseasefree margins and an involved large bowel was performed in 11 cases, with recurrence in the ileum in all cases (IV).

Preoperative complications

During the preoperative disease history various systemic and local complications occurred (II, III, IV).

Systemic complications

The complications, not immediately related to the involved bowel, are listed in table V. From this table one can see, that none of the patients with SBD developed arthritis or complications from the eyes, such as episcleritis or iritis. The most frequent systemic complications in patients with LBD were arthritis and erythema nodosum.

	SBD n=87	LBD n=95
Arthritis	-	14
Episcleritis/ iritis	-	6
Erythema nodosum	2	14
Stunted growth/ sexual retardation	3	4
Amenorrhea	5	4
Biliary stones	3	4
Urinary stones	-	4
Duodenal ulcer	4	5

Table V: Preoperatively occurring systemic complications in 182 patients, subjected to primary resectional surgery

Local complications

Anal fistula was the most frequent local complication (table VI). Such a fistula was seen in seven per cent of the patients with SBD, and in 36% of the patients with LBD.

	<u>SBD</u> (n=87) number of patients	<u>LBD</u> (n=95) number of patients
Anal fistula	6	34
Entero-cutaneous fistula/abscess	6	1
Intraabdominal fistula	-	4
Intraabdominal abscess	-	7
Rectovaginal fistula	-	3
"Kissing" lesion	7	-
Intestinal hemorrhage	2	15

Table VI: Preoperatively occurring local complications in
182 patients subjected to primary resectional surgery

In 16 patients the diagnosis was established at the previous appendicectomy, performed before the major intestinal resection. An entero-cutaneous fistula, between the cecum and the abdominal wall occurred in three patients after the appendicectomy, and another patient developed an intraabdominal abscess involving the abdominal scar as well. The relationships between the macroscopical appearances of the cecum and the removed appendix on one hand, and the occurrence of the above mentioned fistulae/abscess on the other, are seen in table VII. As assessed in this table, the cecum was macroscopically involved in all cases with complications, while

	<u>Cecum</u>		<u>Appendix</u>	
	Macroscopically uninvolved	Macroscopically involved	Macroscopically uninvolved	Macroscopically involved
No complications	6	6	8	4
Enterocutaneous fistula or abscess	-	4	3	1
	6	10	11	5

Table VII: Relations between macroscopical appearances of the cecum and the appendix at the time of appendicectomy, and the development of entero-cutaneous fistulae/abscess after this procedure

the appendix in three of the four patients with complications was grossly free from disease.

In another three patients, not undergoing laparotomy before the primary resection, an abscess around the cecum penetrated the abdominal wall. Incision of the abscess for drainage was done in two of them, after which procedure an entero-cutaneous fistula to the cecum occurred.

The fistulae/abscesses mentioned in no case healed on conservative treatment but were resected en bloc together with the involved bowel segments.

Internal fistulae, between the distal ileum and the sigmoid colon, was seen on preoperative radiography in two patients (IV), and the fistulae were resected together with the invol-

ved bowel at the primary operation.

Small sinuses, penetrating the colonic wall, were seen at radiography in two patients.

Internal fistula or intraabdominal abscess formation, more than mentioned above, did not occur in patients with SBD. Seven of the patients with LBD developed an intraabddominal abscess.

Enchrouchment of the uninvolved sigmoid colon from the diseased distal ileum - "kissing lesion" - was found in seven cases at the time of operation. Six of these patients were operated upon within five months after diagnosis, while the operation in the seventh patient was performed two years after diagnosis.

Intestinal hemorrhage, necessitating blood transfusion, occurred in two patients with SBD and in 15 patients with LBD.

The time of occurrence of the complications after onset of the disease for the 163 patients with preoperatively established diagnosis of Crohn's disease (II) is seen in table VIII. As shown in the table, many of the local complications, such as anal fistulae, intraabdominal fistulae or abscesses and intestinal hemorrhage, developed after more than one year's disease history.

Indications for surgery

Preoperative complications leading to surgery, in relation to the site of involvement and in relation to whether the diagnosis of Crohn's disease was established or unknown at the time of operation, are seen in table IX. In many cases there was a number of conjoined factors that ultimately contributed to the decision of surgical intervention, such as deterioration of the clinical course in combination with the occurrence of an anal fistula, or the occurrence of stunted sexual development. The number of patients in group A, however, operated upon due

Complications	At onset	1 - 5	6 - 11	12 - 23	≥ 24 months	Total no of patients	Percentage of total no of patients	Total %
<u>Systemic</u>								
Arthritis	0 + 4	0 + 1	0 + 2	0 + 1	0 + 2	10	0 + 14	8
Episcleritis/iritis			0 + 1		0 + 1	2	0 + 3	2
Erythema nodosum	1 + 4	0 + 1		1 + 0	0 + 7	14	3 + 16	11
Amenorrhea	1 + 2	1 + 1	1 + 0	1 + 0		7	-	-
Biliary stones	1 + 1	1 + 0		0 + 1	1 + 1	6	5 + 4	5
Urinary stones		0 + 1			0 + 2	3	0 + 4	2
Duodenal ulcer		1 + 1			1 + 2	5	3 + 4	4
Stunted growth/ sexual development						7	-	-
<u>Local</u>								
Anal fistula	1 + 5	0 + 5	2 + 2	1 + 2	2 + 10	30	10 + 33	23
Entero-cutaneous fistulae/abscess		6 + 1				7	10 + 1	5
Intraabdominal fistula/abscess		0 + 1		0 + 1	0 + 3	5	0 + 7	4
Recto-vaginal fistula					0 + 1	1	0 + 1	1
Intestinal hemorrhage	0 + 1	0 + 3		0 + 2	2 + 6	14	3 + 16	11

Table VIII: Preoperative systemic and local complications in relation to time of occurrence in patients with preoperatively known Crohn's disease.

Figures to the left represent patients with small bowel involvement, and to the right patients with mainly or exclusively large bowel disease.

Indication	SBD		LBD		Total number of patients
	Group A	Group B	Group A	Group B	
Weight loss, pain, diarrhoea	39		54		93
Intestinal obstruction		8	1	6*	15
Minor symptom	9		5		14
Anal fistula	4		6	3*	13
Suspected appendicitis		9		2	11
Suspected appendiceal abscess		2			2
Entero-cutaneous fistula/abscess	4		1		5
Intraabdominal fistula/abscess	2		1		3
Rectovaginal fistula				1*	1
Intestinal hemorrhage				1*	2
Stunted growth/sexual development	2		3		5
Fulminant colitis			2	1*	3
Suspicion of malignancy		3		3*	8
Miscellaneous		5		2	7
	60	27	73	15	182

Table IX: Indications for primary operation in 182 patients with Crohn's disease. For abbreviations see text

* Patients treated as having ulcerative colitis

to the formation of internal fistulae or abscesses or due to intestinal obstruction, was small. In 14 patients, in whom there were objective signs of the disease, as seen radiographically or rectoscopically and/or by blood chemistry, the operation was carried out though they had only minor subjective symptoms. These fourteen cases were operated upon during the latter part of the investigation period, and the operation was performed in order to forestall complications, such as those mentioned above.

Primary surgical procedures

Palliative operations

In twelve of the 182 patients the primary major intestinal operation was only palliative (see definitions). The surgical procedures performed are seen in table X (III, IV). In four patients with LBD resection together with the performance of an ileostomy was carried out. One of these four patients got a sigmoidostomy at the same time and the reason for this was to exclude a severely involved rectum.

"Radical" operations

A "radical" resection (see definitions) of the bowel was performed in 170 patients, and the operative procedures are seen in table X (III, IV).

Small bowel resection was carried out in five patients with SBD. As assessed at the reevaluation performed, only four patients, "radically" operated upon, had lesions confined to the proximal ileum. Three of these four patients underwent small bowel resection, while the fourth patient had an ileocolic resection. The remaining two of the five patients, on whom small bowel resection was performed, had lesions in the distal ileum and the cecum as well, a fact which was not known at the time of operation (III). Fifteen patients, with the lesions in both the right and the left colon, were operated upon with an ileocolic resection and anastomosis (IV). The anastomosis in these cases

Operative procedure	<u>SBD</u>		<u>LBD</u>	
	"Radical" resection	Palliative operation	"Radical" resection	Palliative operation
Small bowel resection	5	4		2
Ileocolic resection + anastomosis	77	1	26	1
Ileocolic resection + entero-stoma				3
Colectomy + IRA as a one-stage procedure			11	
Colectomy + temporary ileostomy			11	
Colectomy + permanent ileostomy			29	1
Proctocolectomy			7	
Miscellaneous procedures			4	
	82	5	88	7

Table X: Primary surgical procedures in 182 patients with Crohn's disease
IRA = ileorectal anastomosis

was performed between a macroscopically healthy small intestine, without lesions in the resection margins microscopically, and a large bowel with lesions left behind.

Colectomy with ileorectal anastomosis either as a one-stage (11 patients) or a two-stage procedure (11 patients), was

performed in 22 patients. In another 29 cases, operated upon with colectomy and ileostomy, the restoration of the bowel continuity was never done.

Proctocolectomy was only performed in seven patients, and in six of them the preoperative diagnosis was ulcerative colitis. Thus, only one patient with preoperatively known Crohn's disease of the large intestine initially underwent proctocolectomy.

Early postoperative complications after primary operation

During the first postoperative month after the primary surgical procedure, two patients developed an anastomotic leakage, in one of them after ileocolic resection and in the other after colectomy and ileorectal anastomosis (table XI). One of them was extremely deteriorated at the time of surgery, and the other patient had an ileo-sigmoid fistula. Both died due to sequelae of the anastomotic dehiscence (III, IV).

Intestinal obstruction occurred in 13 patients (7%) and wound infection in 14 patients (8%). An intraabdominal abscess was treated in two patients with SBD and in three patients with LBD. Another patient with SBD developed a pelvic abscess, and a recto-vaginal fistula soon occurred.

Minor septic complications, such as pneumonia or fever more than 38°C of unknown origin, occurred in 19 patients.

At the time of the primary operation, 65 patients had septic complications (fistulae, abscesses, peritonitis). The relationships between the presence or absence of such complications at the time of surgery and the occurrence of early postoperative complications are seen in table XII. One can see that 45% (29/65 patients) with septic complications at operation developed early postoperative complications. The corresponding figure for the remaining patients was 22% (26/117 patients). The difference between the two groups was statistically significant

	<u>SBD</u>		<u>LBD</u>	
	A	B	A	B
	n = 60	n = 27	n = 73	n = 22
Anastomotic dehiscence	1	-	1	-
Intestinal obstruction	2	1	8	2
Intraabdominal abscess	2	-	1	2
Entero-cutaneous fistula	1	-	-	-
Recto-vaginal fistula	-	1	-	-
Intraabdominal hemorrhage	-	-	-	1
Wound infection	2	5	6	1
Ileostomy retraction	-	-	1	-
Minor septic complications	5	7	6	1

Table XI: Complications occurring in the early postoperative period after primary operation for Crohn's disease.

($p < 0.01$). Thus, the occurrence of septic complications at the time of operation correlated to the development of early postoperative complications.

Late complications

During the follow-up time reoperation due to intestinal obstruction had to be carried out in 29 patients, in four of them more than once (table XIII) (III, IV).

New anal fistulae occurred in 18 patients, and in 12 of them this complications was the first symptom of recurrent disease of the intestine. Urinary or biliary stones were recorded in 22 and nine patients, respectively. One patient with SBD later on developed Bechterew's disease. Eight patients were reoperated due to abdominal hernia. Stitch abscesses (non-resorbable suture) were seen in 28 patients.

Early postoperative complications	Patients without septic complications at the time of surgery n = 117	Patients with septic complications at the time of surgery n = 65	Total number of patients with early postoperative complications
Anastomotic dehiscence	-	2	2
Intraabdominal abscess	-	5	5
Intestinal obstruction	8	5	13
Wound infection	4	10	14
Septic fever, pneumonia	12	7	19
Entero-cutaneous fistulae	1	-	1
Recto-vaginal fistula	1	-	1
	26 (22%)	29 (45%)	55 (30%)

Table XII: Early postoperative complications after the primary operation in relation to the occurrence of septic complications at the time of operation (anal and recto-vaginal fistulae included).

	<u>SBD</u>		<u>LBD</u>	
	A	B	A	B
	n = 60	n = 27	n = 73	n = 22
Intestinal obstruction	7	3	14	5
Anal fistula	2	1	13	2
Rectovaginal fistula	-	-	1	-
Urinary stone	7	6	7	2
Biliary stone	3	2	1	3
Duodenal ulcer	1	1	3	2
Bechterew's disease	-	1	-	-
Abdominal hernia	-	1	4	3
Stitch abscesses	6	3	13	6
Entero-stoma problem	-	-	15/41	6/13
Delayed perineal healing after proctectomy	-	-	12/21	4/14

Table XIII: Complications occurring in the late postoperative period
in patients with Crohn's disease.

During the follow-up time altogether 54 patients got an entero-stoma, and 21 of these patients were treated for various problems concerning these stomas. The most common complication was retraction of the ileostomy, seen in 17 patients. Altogether 24 operations had to be performed to correct these complications. Another four patients had to get a new ileostomy due to fistulae, while another patient had to be operated upon due to prolapse of the ileostomy.

In 35 patients the rectum was subsequently excised and in 16 of these 35 patients the healing of the perineal wound was delayed more than three months. (II, IV).

Late mortality

During the follow-up time two patients with LBD died in the early postoperative period after reoperation, one of them due to complications of an anastomotic leakage, and the other in a "hepato-renal" syndrom (table XIV). A third patient with SBD died in pulmonary embolism after a reoperation.

	<u>SBD</u> n = 87	<u>LBD</u> n = 95	Total number of deaths	Percentage of total number of patients
Dead in the early postoperative period after primary operation	1	1	2	1.0
Dead in the early postoperative period after reoperation	1	2	3	1.7 4.4
Dead of intercurrent disease with Crohn- lesions in the bowel	2	3	5	2.8
Dead of intercurrent disease	1	3	4	2.2
	5	9	14	-

Table XIV: Mortality after surgical treatment for Crohn's disease.

Another nine patients died during the late postoperative period. Five of these nine patients had inflammatory lesions in the bowel, as seen at autopsy. Two of them died due to malignancy, one patient due to heart failure and one patient due to insufficiency of the liver. The fifth patient committed suicide.

The remaining four patients died of intercurrent diseases (sequelae of a fracture of the femoral neck, cerebral hemorrhage, tuberculosis and hemorrhage from peptic ulcer). These

four patients had no inflammatory lesions in the bowel at autopsy.

Recurrence

A primary "radical" operation (see definitions) was performed in 170 patients. Two patients died during the first postoperative month, and the recurrence rates were calculated for the 168 patients, surviving the initial operation (I).

During the follow-up period, 85 of these 168 patients had no evidence of recurrent disease. Recurrence developed in 83 patients. Thus, the crude recurrence rate was 49%. The cumulative recurrence rate, calculated according to the actuarial method, was at 15 years 53%.

Some factors, which possibly could influence the development of recurrent disease, were analysed.

Age and sex

There was no difference in the recurrence rates between different age groups at primary surgery or between the sexes.

Duration of the preoperative disease history

In 123 of the 168 patients, the diagnosis of Crohn's disease was preoperatively established (group A) (II). Recurrence occurred in 65 of these patients (53%). As mentioned above, the median time between diagnosis and primary operation for the 57 patients with SBD was four months, and for the 66 patients with LBD eight months (table I).

Eighteen of the 45 patients (40%) in whom the diagnosis of Crohn's disease was unknown at the time of surgery (group B) developed recurrence. In 15 of these cases, preoperatively treated as having ulcerative colitis, the median time between diagnosis and operation was long (3.2 years) (IV), while the duration of the disease history for most of the remaining

thirty patients was short.

There was no difference between the recurrence rates for the patients with preoperatively established diagnosis (group A) and for those with unknown diagnosis (group B), nor was there any difference between the recurrence rates for the patients belonging to group A and group B within the two sublocalizations of the disease (SBD and LBD) (table XV).

The analysis was also performed in another way. The 168 patients were divided into two groups, according to the total length of the disease history. The first group consisted of 70 patients with a total disease history less than one year and the second group of the remaining 98 patients with a disease history of more than one year. Fortysix per cent (32/70 patients) of the patients in the first group developed recurrent disease, while 52% (51/98 patients) belonging to the second group developed recurrence. The cumulative recurrence rates at 15 years was 46% and 56%, respectively. There was no statistical difference between the recurrence rates for these two groups.

Thus, the duration of the preoperative disease history had no influence on the recurrence rate.

Extent of the lesions

Recurrent disease occurred in 42% of the patients with SBD (34/81 patients), while the corresponding figure for the 87 patients with LBD was 56% (49/87 patients). The cumulative recurrence rates at 15 years were 43% and 62%, respectively (table XV). There was no statistical difference between the two main localizations of the disease, neither when calculated from crude figures, nor when computed according to the life table method.

	<u>SBD</u>		<u>LBD</u>	
	A	B	A	B
	n = 57	n = 24	n = 66	n = 21
Number of patients with recurrence	26	8	39	10
Crude recurrence rate %	47	33	59	48
	42		56	
Cumulative recurrence rate at 15 years %	43 ^{*)}		62	
Number of patients with second resection	13	5	29	9
Crude rate second resection %	23	21	44	43
	22		44	
Cumulative probability of a second resection at 15 years %	28 ^{*)}		47	

Table XV: Recurrence rates and cumulative probability of having a second resection in relation to the extent of the lesions in the bowel.

^{*)} Four patients with lesions proximal to the distal ileum not included.

Thus, the recurrence rates were not influenced by the extent of the lesions in the bowel.

In relation to surgical procedures

When "radical" resection of the bowel is performed, the operations largely reflect the site of the disease. Fortynine of 102 patients (48%), operated upon with ileocolic resection and anastomosis (see definitions) developed recurrence. As mentioned above, however, in 15 of these cases lesions in the left part of

the colon were left behind for various reasons, and a resection with anastomosis between a macroscopically disease-free small intestine and a diseased colon was performed. Recurrent disease in the ileum occurred in all these 15 patients.

Colectomy with ileorectal anastomosis was carried out in 22 patients. One of the 11 patients, who had the ileorectal anastomosis performed at the primary operation, died in the early postoperative period.

Six of the remaining 10 patients developed recurrence in the small bowel, adjacent to the anastomosis.

Another 11 patients underwent colectomy and ileorectal anastomosis as a two-stage procedure. In two of them, however, this procedure was carried out at the reoperation for recurrence. Recurrent disease in the ileum developed in five of the remaining nine cases.

There was no statistical difference in the recurrence rates between any of the operative procedures performed. Thus, different surgical procedures had no influence on the recurrence rates.

Histopathological appearance of the resection margins

The relation between the microscopical appearance of the resection margins and recurrent disease was analysed. The patients were divided into three groups according to whether there were no lesions, major lesions (ulcers, crypt abscesses and/or giant cell granulomas) or minor lesions (increased number of inflammatory cells in the mucosa or the submucosa).

Two groups of the patients were investigated. The first group consisted of 110 patients, subjected to resection with anastomosis, of whom histological sections from both margins were available. It was found, that the frequency of recurrence was higher in patients with major lesions than in patients without

lesions or with minor lesions. This difference was statistically significant, when calculated from crude figures ($p < 0.01$ and $p < 0.05$, respectively). When calculating according to the actuarial method, there was a statistically significant difference at 10 years, but not at 15 years (I).

This analysis was done, irrespective of the site of involvement of the disease. Therefore, available histological sections from 69 patients with the disease confined to the distal ileum and the cecum were analysed (I). It was found that only eight patients had major lesions in any or both of the resection lines, and in six of them recurrence occurred. Thirtythree per cent of the patients without lesions and 36% of the patients with minor lesions developed recurrent disease.

Thus, the histopathological appearance of the resection margins influenced the recurrence rates.

Postoperative radiography

Eight patients, with recurrent disease developing soon after the primary operation, were reoperated upon due to clinical signs of recurrence, but without radiological examination of the bowel (XVI). Another patient refused radiography. Two patients underwent examination of the large bowel only. In the remaining 157 patients the small bowel was examined. In one of the 157 patients no conclusive examination could be achieved, and in another patient, with ileorectal anastomosis, the recurrence, detected at sigmoidoscopy, could not be seen on radiograms.

Large bowel examination was performed in 97 of the 111 patients with most or entire colon left after the primary operation.

The recurrence was seen on the first technically satisfactory, and thus conclusive, radiography of the small bowel in all 75 patients but five. Thus, the first postoperatively performed

Radiology	Patients without recurrence n = 85	Patients with recurrence n = 83	Total number of patients
Small bowel examination, conclusive	81	74 [*]	155
Small bowel examination, not conclusive	1	-	1
Small bowel examination, recurrence not seen	-	1	1
Large bowel examination	43	54	97
Large bowel examination only	2	-	2
Reoperation without radiological examination	-	8	8
Refused radiological examination	1	-	

* All but five showed recurrence

Table XVI: Postoperative radiological examinations of the bowel after primary "radical" operation.

conclusive radiological examination had a prognostic implication, since a radiography with normal findings indicated a low risk of recurrence.

Twenty of the 74 patients with recurrent disease seen on radiograms had no subjective symptoms of the recurrence at the time of radiography. During the follow-up time, eight of these 20 patients with "radiological recurrence" developed clinical signs of recurrent disease, while the remaining 12 patients had no

symptoms of recurrence at the latest clinical check-up.

Reoperation and second recurrence

Reoperation due to recurrent disease was performed in 62 of the 83 patients with recurrence. In 56 of the 62 patients a second resection of the bowel was carried out. As seen in table XVII, the risk of having a second resection was smaller for patients with SBD than for patients with LBD, when calculated from crude figures. When computed according to the actuarial method, there was no difference at 15 years (I).

Considering the risk of having a second resection in relation to the microscopical appearance of the resection margins, there was a statistically significant difference, both when calculating from crude figures and according to the actuarial method. The risk of having a second resection was greater for patients with major histopathological lesions than for those without lesions or with minor lesions in the resection lines.

After the second "radical" operation 13 of 18 patients (72%) with SBD and 11 of 33 patients (33%) with LBD developed recurrent disease again. The difference was statistically significant ($p < 0.05$). The cumulative recurrence rates at ten years were 81% and 36%, respectively and when computed according to the actuarial method this difference was also significant (I).

Fate of the rectum

At the time of the initial surgical procedure, 50 patients had lesions in the rectum (table III and IV). In addition, 10 patients developed rectal lesions during the follow-up time. In 35 of these 60 patients, the rectum had to be excised later on, while it was left in the remaining 25 patients. The involved rectum did not heal after primary colectomy and ileostomy (IV).

	<u>SBD</u> n = 77 ^{*)}	<u>LBD</u> n = 87
Second resection	16	38
		
Crude rate second resection %	21	44
Cumulative probability of a second resection at 15 years %	28	47

Table XVII: Frequency and cumulative probability of having a second resection for recurrence of Crohn's disease.

S = Chi square = 8.7 p<0.01

*) Four patients, with lesions confined to the small bowel, proximal to distal ileum, excluded.

Eleven of the 21 patients, surviving colectomy and ileorectal anastomosis, developed recurrence (5 patients) or relapse of persisting disease (6 patients) in the rectum. Proctectomy was subsequently performed in seven of these eleven patients, while the rectum was left diseased in the remaining four. Two of these four patients preferred to keep the continuity of the bowel.

Nine of the 10 patients without recurrence in the ileum had no rectal lesions at the time of the performance of the ileorectal anastomosis.

Quality of life

At the latest clinical examination, which in all surviving patients was performed during the latter part of 1978 or during 1979, most of the patients (79%) were found to do well (QL I) (table XVIII). Thirteen per cent of the patients were judged

QL	SBD n = 82	LBD n = 86	Total number of patients n = 168
I	68 (83%)	65 (76%)	133 (79%)
II	10 (12%)	12 (14%)	22 (13%)
III	2 (2%)	5 (6%)	7 (4%)
Recently reoperated	2	4	6

Table XVIII: "Quality of life" in 168 patients, alive at the latest clinical examination.

to do less fair (QL II) due to diarrhoea, pain etc or due to intercurrent disease. Four per cent (seven patients) were in a poor state of health (QL III) due to recurrent disease or extensive loss of intestinal fluid. There was, however, no patient with serious metabolic disturbances, and none of the patients had to be treated with continuous parenteral nutrition.

II. PATIENTS WITH THE DISEASE CONFINED TO THE APPENDIX VERMIFORMIS.

During the period of investigation, twelve patients, operated upon, were found to have Crohn's disease limited to the appendix (V). Six of them had a short disease history, between one and three days, while another three were preoperatively treated during a couple of months for a presumed appendiceal abscess. The remaining three cases had longer histories, between six months and two years.

At the laparotomy, the appendices were conspicuously enlarged and the wall thickness ranged between one and two centimeters. In most of the specimens there were ulcerations of the mucosa. At microscopy, non-caseating granulomas, without microabscesses, were found in 11 of the 12 specimens, while transmural inflammation with fibrosis and oedema was seen in all cases.

Early postoperative complications occurred in two patients, (intraabdominal abscess and wound infection, respectively). Fistula formation from the cecum, or from any other part of the bowel, did not occur.

Seven of the 12 patients were postoperatively examined by radiography of the small (six patients) and the large bowel (seven patients), without evidence of inflammatory lesions. The remaining five patients were asked by mail concerning their state of health after the operation. The outcome after a median follow-up time of almost fourteen years was excellent in all cases but one. This patient suffered from sequelae of an intracerebral hemorrhage. None of the patients had had further manifestations of the disease.

III. PATIENTS NOT OPERATED UPON

During the investigation period, 13 patients were diagnosed but not operated upon with bowel resection(II). In three cases the diagnosis was based on radiological examinations only. One of these three patients had lesions in the distal ileum and the right hemicolon, while the other two had lesions in the entire colon as well. One of them was treated with corticosteroids and sulphasalazine for periods, while another patient was treated with corticosteroids in combination with azathioprine during six years. The third patient was treated with sulphasalazine for a short period. In all these three patients the

disease showed regression in the large intestine, as seen at radiography, and in one of them the lesions had disappeared completely after six years. None of them was on medicament treatment at the latest clinical examination, and all of them were doing well (QL I).

In the remaining 10 patients the diagnosis was assessed at radiography, and supported by the findings at histopathological examinations of biopsies taken at sigmoidoscopy (six cases), at explorative laparotomy (three cases) or at appendicectomy (one case). The diagnosis was supported by the finding of giant cell granulomas in all cases but one. This latter patient was initially thought to have ulcerative colitis.

The extent of the lesions at the time of diagnosis, as assessed at the reevaluation, is seen in table XIX. Three patients underwent resection of the bowel during the follow-up time and in one of them, operated upon with colectomy and ileorectal anastomosis, recurrent disease in the small bowel occurred.

Extent	Number of patients
Duodenum	1
Small bowel	2
Distal ileum	1
Distal ileum + right colon	1
Distal ileum + colon, including rectum	5
Colon only, including rectum	1
Rectum only	2

13

Table XIX: Extent of the lesions, as assessed at the reexamination, in patients not operated upon during the investigation period.

At the latest clinical check-up, six of the 10 patients were doing well, while another patient, on continuous treatment with corticosteroids and azathioprine, was doing less fair (QL II) due to general weakness and diarrhoea. One patient had a follow-up time less than six months after operation and "quality of life" was not evaluated. The remaining two patients, the patient with lesions in the duodenum and one patient with rectal lesions only, were lost to follow-up.

GENERAL DISCUSSION

Crohn's disease is a peculiar disease with unknown etiology. The treatment, therefore, varies widely, but no therapeutic attempt is particularly successful in terms of curing the disease. Comparatively satisfactory results of different conservative methods have been reported, but still the majority of the patients sooner or later needs to be operated upon, due to, for example the development of fistulae or abscesses, or due to deterioration of the clinical condition. In order to find out more clearly when and how patients with Crohn's disease shall be operated upon, randomized controlled investigations are desirable. Such studies can, and have been, performed in order to analyse the effect of conservative treatment, but not of surgical therapy. Interpretation of data are, however, often difficult since the disease occurs in so many shapes that patients grouped together are often not quite comparable. Another problem is the variation in disease activity, which leads to exclusion of many patients from the treatment they have been allocated to. These problems seem difficult to overcome, not least from an ethical point of view. Therefore, analyses of total, unselected materials are necessary.

The present series of patients consists of all residents in the population of the city of Malmö, who were diagnosed as having Crohn's disease during the period of investigation. There was no selection of patients. The data concerning diagnosis, treatment and follow-up are complete in all cases but two. Thus, it was possible to obtain a complete survey of the disease in the city.

Histopathologically, the diagnosis of Crohn's disease is almost firm when the pathologist is able to demonstrate the most distinctive feature of the disease, the non-caseating

giant cell granuloma. In the present series, such granulomas were seen in 84% of the resected specimens. In other reports the frequencies range between 23% and 87% (84,87,88,89). The possibility of detecting this feature is highly correlated to the number of examined histological sections of the specimens. It has, therefore, been recommended to prepare several histological sections, and to take multiple biopsies (73), which was done in the present study.

The analysis showed that Crohn's disease predominantly involving the large bowel was common and seen in half of the cases. Such a high frequency of Crohn's colitis has been reported by others in recent years (90,91,92), but earlier the reported predominant localisation was the small bowel (1,87,88,93,94). Crohn's disease of the colon has been generally recognized after the report by Lockhart-Mummery & Morson (1960) (28). The high frequency found in the present series as well as in those quoted may indicate an increased incidence. Other reasons could be previous misinterpretation of diagnostic findings or lack of distinctive features. The difficulties in diagnosing Crohn's disease are illustrated by the finding in the present series that 15 patients were preoperatively regarded as having ulcerative colitis, and that five of them even after the operation for some time were considered as having ulcerative colitis.

The policy in the present series was to operate upon the patients early. It could be argued, that many patients operated upon early, will experience side-effects of resection, such as increased number of loose stools, or even an ileostomy. They may also get metabolic disturbances, such as decreased resorption of vitamin B₁₂ and increased loss of bile acids. Such disturbances are well recognized results of major resection (95). The relative importance of these side-effects are, however, difficult to objectively compare with those of con-

servative treatment including the effects of the ongoing inflammatory process. The decision when to operate upon a patient with Crohn's disease often remains difficult, and in every case the pros and cons must be carefully considered.

The preoperative disease history for the patients in the present study was short (median time:SBD = 1.3 years, LBD = 1.8 years), when compared to other reports. Thus, Lennard-Jones & Stalder (1967) reported a mean duration of five years for 78 patients with predominantly small bowel involvement (30). de Dombal et al (1971) reported that 54% of their patients had a disease history of more than two years (31). In the report by Steinberg et al (1974), the mean interval from onset to operation in 73 patients with predominantly colonic disease was 6.1 years (12). The median time of the disease history for the patients, reported by Nygaard & Fausa (1977) was four years (96). Lock et al (1981) reported a mean time of 5.8 years for patients with mainly colonic involvement (97). It is thus apparent that surgery in the present series was performed comparatively early.

In the present series the frequency of serious preoperative complications in the patients with preoperatively established diagnosis (II) was low, compared to those in several other reports (1,2,36,92,94,98,99,100,101). Thus, Farmer et al (1976) (4) reported that 20% of their cases with Crohn's disease of the colon had fulminant colitis, which was only seen in two percent in the present series. Farmer et al also reported that internal fistulae and abscesses indicated surgery in 32% and 52%, respectively, depending on whether the predominant involvement of the bowel was in the colon or in the ileum. Such complications were only seen in about five percent of the patients in the present study, and most of them developed in patients with predominantly large bowel disease. Arthritis was not seen in any cases with mainly small bowel

involvement in the present study. Rankin et al (1979) reported that this complication occurred in 18% in patients with mainly small bowel disease (102).

The frequency of complications developing in the early post-operative period was also low in the present study. Allsop & Lee (1978), Fasth et al (1980) and Higgins et al (1980) found that the frequency and severity of early postoperative complications was highly correlated to the presence of septic preoperative complications (9,103,104). This was also the finding in the present study. The frequency of early post-operative complications was significantly higher in patients with septic complications at the time of surgery than in those without such complications at the time of the primary operation. It therefore seems warranted to recommend that surgery should not be delayed to a stage, where such complications occur.

The early postoperative mortality rate (1%) in the present study was lower than most of the reported rates (7,12,38,40, 54), but in accordance with that reported by Fasth et al (1980) (9). The overall late mortality rate was 6.6%. Three patients died early after reoperation, while five of the remaining nine patients, who died of intercurrent disease, had Crohn-lesions in the bowel, as seen at the autopsy (4.4%). This late mortality rate corresponded to that reported by Kåresen et al (1981) (105), but was lower than those in other reports (7,12,36,38,106).

The choice of operative procedures has also been a matter of dispute throughout the years. Some surgeons prefer by-pass procedures with or without exclusions of the involved bowel. It has, however, been convincingly shown that the recurrence - or rather relapse - rate after such operations is higher than after resectional surgery (79). The aim of resectional

treatment is to remove the localized process, but this is not applicable in all cases. There are, however, some patients palliatively operated upon who in spite of disseminated lesions in the bowel are getting on rather well, and there are a few such patients, in whom the disease shows regression or even resolution. These circumstances, however, do not justify a totally reluctant attitude towards surgery, hoping that the disease subsequently will "burn out" and disappear. According to many reports most patients do need an operation sooner or later, due to complications (36,38,53,90,94).

Krause (1978) and Hellberg et al (1980) advocate resection of the bowel with a macroscopically disease-free margin of 10-15 cm, a policy similar to that in the present series (34,54). Since the site of the recurrence after such procedures is in most cases the proximal side of the anastomosis (80), extended resection of the macroscopically uninvolved large intestine seems to be unnecessary in cases with Crohn's disease confined to the distal ileum, with or without involvement of the cecum.

Some patients, without preoperatively known diagnosis of Crohn's disease, were operated upon with the presumptive diagnosis of appendicitis or appendiceal abscess. After appendicectomy in patients with Crohn's disease, there is a high risk of fistula formation between the bowel and the abdominal wall. According to some authors appendicectomy is safe in this situation, provided that the cecum is uninvolved (1,107,108,109,110). If a fistula develops it originates from the involved distal ileum and not the base of the appendix in the cecum (108,111,112). Fonkalsrud et al in 1982, however, concluded that the appendix should rarely be removed due to the high risk of complications (113).

The finding in the present study, that fistula formation from the involved cecum occurred in four patients out of ten after

appendicectomy, indicates that this procedure should be avoided if the cecum is affected by Crohn's disease, and if it is decided to postpone the intestinal resection. It is, however, necessary to consider other disorders affecting these parts of the bowel with macroscopical features which may resemble Crohn's disease, for example infection by *Yersinia enterocolitica* (114,115) or *Yersinia pseudotuberculosis* (116) (V). In these disorders appendicectomy should be performed.

Crohn's disease *confined* to the appendix seems to be a rare entity. Only a few cases are reported in the literature (V). At this hospital, where the general policy has been to examine specimens from appendicectomy histopathologically, only 12 cases with lesions suggesting Crohn's disease were found. The histopathological diagnosis came as a surprise. As discussed by Payan et al in 1981 there are other granulomatous diseases than Crohn's disease, affecting this part of the bowel, such as tuberculosis, sarcoidosis and infection by *Yersinia pseudotuberculosis* (117). Therefore, postoperative bacteriological culture and serological tests should be performed in these cases. If the results of these examinations are negative, the diagnosis of Crohn's disease is most likely, and radiography of the bowel should be done in order to reveal any other extent of the disease. Crohn's disease of the appendix seems to be a mild form of the disease since only a few of the reported patients, and none of the present patients, developed recurrent disease in other parts of the bowel.

In previous reports it has been discussed whether the rectum should be preserved or not (33,54,118,119,120,121,122,123,124). The main argument for leaving the rectum is that it might be possible to perform an ileorectal anastomosis, either as a primary or as a secondary procedure. Another argument is avoidance of complications after proctectomy, such as damage

to the pelvic nerves (54,125) and delayed perineal healing (121,123,126,127).

Arguments against preservation of the rectum are, firstly, the finding that the risk of recurrence in the small bowel as well as in the rectum after colectomy and ileorectal anastomosis is high, especially if the rectum is primarily involved. Another argument against preservation is that the inflammation in the rectum subsequently may affect neighbouring structures, such as the vagina or the bladder. Thirdly, there seems to be a risk of malignant transformation in an excluded rectum (97,128).

In the present study, about 40% of the patients remained disease free after subtotal colectomy and ileorectal anastomosis (primary or secondary). The recurrence rate of 60% was in agreement with those reported by others (118,119,120,121, 123,124). When the rectum was primarily uninvolved, the procedure was successful in 2/3 of the patients. If the rectum, however, was involved at the time of operation, the outcome was poor. It is concluded that subtotal colectomy and ileorectal anastomosis is a procedure worth trying in cases without involvement of the rectum. This procedure will give the patients, especially those of younger age, time and possibility to settle down socially, even if proctectomy has to be carried out later on due to recurrent disease. On the other hand, if there are pronounced lesions in the rectum, proctectomy seems to be preferable, especially in older patients (IV).

After the operation the patients should be closely followed. Repeated clinical check-ups, which include sigmoidoscopy with biopsy and blood chemistry, should be performed in order to reveal relapse of the disease and to enable correction of metabolic disturbances. During the first postoperative years,

radiography of the bowel is important. As shown in the present study, the first conclusive radiological examination of the small bowel may have a prognostic implication. If there are no lesions seen, the risk of recurrence seems to be low, at least within a median observation time of ten years.

The overall crude recurrence rate after the primary operation in the present study was high, 49%, and the cumulative recurrence rate, calculated according to the life table method, was 53% at 15 years (I). The reported recurrence rates after resectional surgery vary widely. Nugent et al in 1973 reported a recurrence rate of three percent after proctocolectomy, while Steinberg et al (1974) found that all patients developed recurrent disease after subtotal colectomy and ileostomy, when calculated according to the actuarial method (11,12). In many previous reports it has been found, that the risk of recurrence after the initial operation is highest in patients with ileocolitis (35,52,92), while patients with Crohn's disease confined to the large bowel are less prone to develop recurrent disease.

In the present study, however, there was no such relation between the localization of the lesions in the bowel at the primary operation and the recurrence rate, and this finding was in agreement with that reported by Hellberg et al (34).

After a second "radical" resection, however, it was found that almost 75% of the patients with mainly or exclusively small bowel disease developed recurrence (III). This rate was significantly higher than the recurrence rate in the patients with predominantly large bowel disease. Such a discrepancy has also been reported by others (1,30,33).

When intentionally "radical" resections are performed, the type of operation largely reflects the extent of the disease

in the bowel. As demonstrated in the present investigation, the operative procedures employed had no influence on the recurrence rate (I), and a similar finding has been reported by Hellberg et al (34).

The duration of the preoperative disease history had no influence on the recurrence rate, a finding which is in accordance with others (33,34,52,94,106). Schofield (1965) and Steinberg et al (1974), however, have reported that patients with a short history were more susceptible to develop recurrent disease than patients with a longer preoperative disease period (12,93).

Age at the time of operation did not influence the recurrence rate, a finding consistent with those reported by others (30, 34,35,52,96,106,129). Stahlgren & Ferguson, Atwell et al, de Dombal et al, Steinberg et al, Hellers and Cooke et al, however, have reported that the risk of recurrence was higher in younger patients (12,31,33,38,94,130).

The only factor, which was found to be related to the occurrence of recurrent disease, was the histopathological appearance of the resection margins. Contrary to the report by Pennington et al (1980) (131) and Lee & Papioannou (1980) (85), it was found that the frequency of recurrence was significantly higher in patients with ulcers, crypt abscesses and/or granulomas in the resection lines than in those without lesions or with only minor lesions, such as increased number of inflammatory cells in the mucosa or the submucosa. The same finding has also been reported by Kåresen et al in 1981 (105). This further emphasizes the importance of peroperative naked-eye inspection of the bowel. No data are available saying that wider excision can reduce the recurrence rate, but analysis of the lines of excision may be used for prognostic estimation of the recurrence risk in the particular patient.

The comparatively early surgery performed in the present series, thus led to low postoperative complications and mortality rates. The final outcome, expressed in terms of "quality of life", was comparable to other reports (7,38,53). The frequency of serious preoperatively developing complications, however, was noticeably low. Even if the recurrence rate after surgery is depressingly high, and not changed by early surgical intervention, this fact should not act as a deterrent. After resection some 40% seem to have no further manifestations of the disease, at least within a median observation time of ten years, according to the findings in this series. The number of disease-free patients will further increase after reoperation for recurrence.

Early resectional surgery, "radically" performed, thus seems to be justified as part of the treatment of Crohn's disease. This disease, however, has many aspects, and our knowledge is still limited. Further investigations concerning etiology as well as further experiences from different forms of treatment and the outcome after real long follow-up time are necessary.

MAIN CONCLUSIONS

- 1 Crohn's disease predominantly involving the large bowel was as common as Crohn's disease predominantly involving the small bowel.
- 2 The preoperative and early postoperative complication rates as well as mortality were low in the present series.
- 3 The overall recurrence rate was close to 50%, both when calculated from crude figures and according to the actuarial method.
- 4 The recurrence rate after colectomy or proctocolectomy was not lower than that after ileocolic resection.
- 5 The recurrence rate was not influenced by age at the time of operation, sex, duration of the preoperative disease history, early surgery or the extent of the lesions in the bowel.
- 6 The histopathological appearance of the resection margins seems to have prognostic value regarding the recurrence rate.
- 7 The risk of recurrence in the small bowel was great when anastomosed to a large bowel with lesions left behind. Therefore, repeated preoperative radiography of the large bowel is important in order to reveal such lesions.
- 8 A negative finding at a conclusive early radiography of the small bowel seems to indicate a low risk of recurrence.

- 9 Subtotal colectomy and ileorectal anastomosis seems to be a procedure worth trying if the rectum is apparently uninvolved.
- 10 Rectal lesions did not disappear after diversionary surgery.
- 11 Crohn's disease confined to the appendix vermiformis has a favourable prognosis.

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I

RECURRENCE RATE AFTER SURGICAL TREATMENT FOR CROHN'S DISEASE

by

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ABSTRACT

In a total, unselected series of 207 patients with Crohn's disease diagnosed in 1958 - 1974, 170 were "radically" resected. Two patients died during the first postoperative month. The crude recurrence rate was 49%. The cumulative recurrence rate, calculated according to the actuarial method, was at 15 years 53%. Age, sex, length of preoperative disease history, extent of the lesions in the bowel or primary surgical procedures performed had no influence on the recurrence rates. However, the histopathological appearance of the resection margins seemed to influence the prognosis. The risk of having a second resection was greater for patients with predominantly colonic disease compared to those with mainly or solely small bowel lesions. An early postoperative small bowel radiography with normal findings indicated a low risk of recurrence.

INTRODUCTION

The recurrence rates after surgical treatment for Crohn's disease range from a few per cent to 100% in published reports (1-7). The reasons for this wide range may be that recurrence has been defined in different ways, that the patients have been selected or that the surgical procedures performed have been more or less radical resections or even palliative operations. The accuracy of the follow-up and search for recurrences may have been different.

During the last decade many authors have pointed out that crude recurrence figures give a too low rate and are misleading in evaluation of the prognosis following surgery (4,8-13). A more reliable evaluation is said to be achieved if the statistical analysis according to the actuarial method (14,15) is used, especially when the observation time is short. This method, also called the life table method, gives the annual risk of recurrence as calculated from those followed up and at risk.

With few exceptions (12,16) published studies have been retrospective. The present study reports the results of a series of unselected, consecutive patients, from the city of Malmö, Sweden, operated upon during the years 1958 through 1974. During the first few years of the investigation period patients were operated upon only when complications, intractable on conservative treatment, occurred, but gradually the policy was changed in favour of earlier surgery.

The purpose of the study was to elucidate the recurrence rate in relation to 1/ the duration of the preoperative disease history, 2/ different extent of the disease in the bowel, and 3/ different types of "radically" operative procedures. It was also aimed to study 4/ how soon the recurrences appeared

and 5/ the frequency of resection for recurrence. Finally 6/ the prognostic implication of the histopathological appearance of the resection margins was analysed.

Definitions

1. *Radical resection*: all macroscopically involved intestine has been resected, except for any lesions in an excluded rectum, as assessed at the time of the operation.
2. *Palliative operation*: part of the involved intestinal tissue was resected, or the involved intestine by-passed or excluded.
3. *Ileocolic resection*: ileocecal resection or right hemicolectomy, or resections after such procedures.
4. *Recurrence*: the appearance of objective signs - defined radiologically, endoscopically or histopathologically - of Crohn's disease in the bowel of a patient who has previously had a resection of all macroscopically diseased tissue (the Cape Town classification) (17).

PATIENTS AND METHODS

All patients diagnosed as having Crohn's disease in the defined population of Malmö, Sweden, during the years 1958 through 1973 were traced by Brahme et al (18) in an epidemiological survey. With the addition of the corresponding patients from the following year and after reexamination as described below, altogether 207 patients were found to have Crohn's disease, diagnosed during 1958 through 1974. From the total series 37 patients were excluded for the following reasons: 13 patients were conservatively treated, 12 patients were palliatively operated upon and another 12 patients had the disease confined

to the appendix vermiformis.

In the remaining 170 patients, the primary operative procedure was a "radical" resection. Two patients died in the early post-operative period due to anastomotic leakage, thus there remained 168 patients for this study.

There were 73 males and 95 females. The age of the patients at the time of the primary operation ranged from 10 to 79 years, with most of them, 107 patients, between 16 and 30 years of age (fig 1). The median age was 24 years, the mean age 28 years.

The extent of the disease in the bowel, as assessed at the reevaluation, is shown in table I, from which is seen that 77, or less than half of the patients, had the disease predominantly confined to the distal ileum, with or without lesions in the cecum. In 13 cases the lesions were confined to the large bowel, while mainly colonic involvement with coexisting lesions of various length in the distal ileum was seen in 74 patients.

The operations performed are seen in table II. The most common procedure was an ileocolic resection. In 20 cases the primary operation was performed as an emergency or urgent one, without any preoperative radiographical examinations.

The policy was to open the surgical specimens during the operation and examine them in order to avoid resection in macroscopically diseased intestinal segments. After preparation the specimens were measured and macrophotographed in all cases except for those operated upon during the first few years of the investigation period. The bowel specimens were then fixed in 10% formalin solution on large specially made trays to preserve as good morphology as possible. After fixation a large number of histological sections from the bowel and lymph nodes were

No of patients

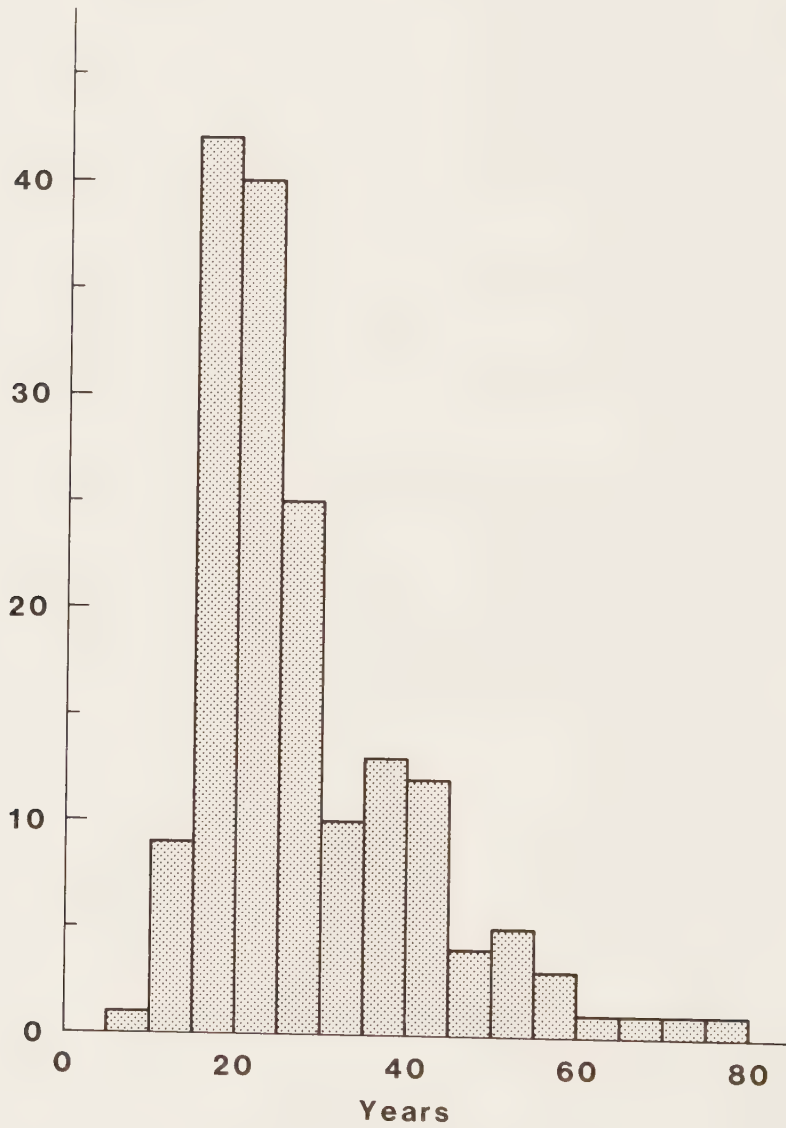


Fig 1: Age at the time of primary operation in patients, "radically" resected for Crohn's disease.

prepared and examined.

All patients were examined postoperatively at Malmö General Hospital, but 22 patients later on moved out from the city and were checked up elsewhere. The results of those examinations were included in this analysis. The patients were examined with regular intervals, and the purpose was to examine them more often during the first postoperative year, including radiological examinations. Later on most of the patients were examined yearly. All patients underwent postoperative radiographical examinations except eight, who were reoperated upon early due to symptomatic recurrence, and one patient who refused radiography.

Nine patients died during the follow-up period, five patients in Crohn's disease and the remaining four of intercurrent disease. Autopsy was performed in these patients except one.

At the end of the follow-up period, December 31st 1979, the median time between the primary procedure and the latest clinical examination or the date of death was 9.3 years (mean 10 years, range 9 months - 19.7 years).

All cases were reevaluated and judged by the authors, i.e. four surgeons, one radiologist (JH) and one pathologist (CL). Since all radiographic films, histopathological sections from biopsies and specimens and, since 1969, the complete specimens have been kept, all cases could be scrutinized thoroughly. Special attention was also paid to the microscopic appearance of the resection margins.

The diagnosis was verified histopathologically in all patients, using the criteria reported by Lockhart-Mummery & Morson (19) and by Price & Morson (20). The radiographic criteria used were those reported by Sellink (21), Laufer (22) and Hildell (23).

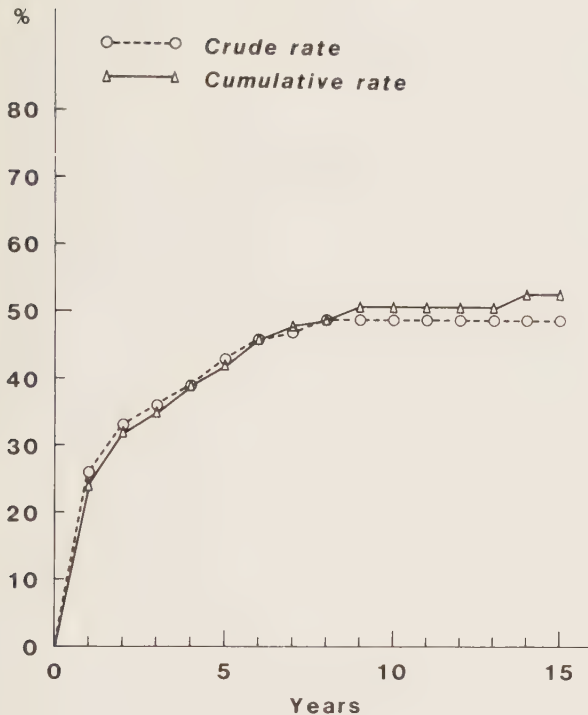
In addition to crude recurrence rates, cumulative recurrence rates were also calculated, using the actuarial method or life table method, described by Hill in 1966 (14) and Andersen & Bonnevie in 1971 (15). The data were analysed with a computer giving estimated recurrence rates and the limits of the 95% confidence interval for each of the postoperative years. Differences between crude rates were evaluated by means of Chi square tests. A p-value less than 0.05 was considered to indicate a significant difference.

In the legends of the figures N stands for number of patients operated upon and n for number of patients at the beginning of the last follow-up year.

RESULTS

During the follow-up period 85 of the 168 patients had no evidence of recurrent disease, while 83 patients developed recurrence. Thus, the crude recurrence rate was 49%. The calculated cumulative recurrence rate was at ten years 51% and at 15 years 53% (fig 2). There was no difference in the recurrence rates between the sexes or between different age groups at initial surgery.

Eight of the 83 patients with recurrence after the primary operation were reoperated upon due to clinical symptoms without radiological examinations. Postoperative radiography of the small bowel was performed in 157 cases. In one of them, without clinical signs of recurrence, the examination was not conclusive. In another two patients only large bowel examinations were done. One patient refused radiography.



Year	No of patients	%	% S.E.
1	43	26	24
2	56	33	32
3	60	36	35
4	66	39	39
5	72	43	42 ± 8
6	77	46	46
7	79	47	48
8	82	49	49
9	82	49	51
10	82	49	51 ± 8
11	82	49	51
12	82	49	51
13	83	49	51
14	83	49	53
15	83	49	53 ± 9

Fig 2: Crude and cumulative recurrence rates in patients with Crohn's disease, subjected to primary "radical" resection.

SE = 2 standard errors of the recurrence rate

$N^{\Delta} = 168$ $n^{\Delta} = 20$

The first technically satisfactory radiological examination of the small bowel was performed during the first postoperative year in 76 cases, during the second year in 32 and during the three following years in 30 cases. In the remaining 18 patients the first conclusive examination was performed after more than five years after the operation.

The recurrences were seen on the first conclusive small bowel examination in all 75 cases but six. In one of these six

patients, with ileorectal anastomosis, the recurrence was detected at sigmoidoscopy but it could not be seen on radiograms.

Fifty-four of the 74 patients were examined due to symptoms, but the remaining 20 patients had no symptoms at all when the first postoperative radiological examination was performed. Later on eight of these 20 patients with "radiological recurrence" developed clinical signs of recurrence. The median time between the first radiographical examination and the occurrence of subjective symptoms in these eight patients was 1.8 years (mean 3.8 years, range 5 months - 16.3 years). The remaining 12 patients with radiological recurrence were at the latest clinical examination still free from symptoms (median 8.7 years, mean 8.8 years, range 4.3 - 15.7 years).

After the second "radical" resection radiological examination of the small bowel was performed in all patients, and a second recurrence could be seen on the first conclusive examination in all 24 patients.

RECURRENCE RATE IN RELATION TO LENGTH OF PREOPERATIVE HISTORY

In 123 patients the diagnosis was established preoperatively while in the remaining 45 cases the diagnosis was unknown at the time of the primary operation. Since these latter patients were not treated as having Crohn's disease they were excluded from this part of the study. Details about these patients will be published in forthcoming reports (III, IV).

The median time between diagnosis and primary operation for these 123 patients was four months for patients with predominantly small bowel disease and eight months for patients with predominantly colonic involvement.

The crude recurrence rate was 53% (65/123 patients).

The cumulative recurrence rate at ten years was 54%. Thus, the recurrence rate for patients, operated upon comparatively early did not differ from that of the whole series.

RECURRENCE RATE IN RELATION TO THE EXTENT OF THE DISEASE

The crude recurrence rates according to the different localisation of the lesions in the intestine at the primary operation are seen in table I. In four patients the disease was confined to the small bowel proximal to the distal ileum, two of them developed a recurrence.

In 77 patients the disease was confined to the distal ileum and the cecum. Recurrence developed in 32 of these patients. Thus, the crude recurrence rate was 42%. The cumulative recurrence rate was at 15 years 43% (fig 3).

Forty-nine of 87 patients with the disease mainly (74 patients) or solely (13 patients) confined to the large bowel developed recurrent disease, a crude recurrence rate of 56%. The cumulative recurrence rate was at 15 years 62% (fig 3).

There was no difference between the recurrence rates for patients with Crohn's disease mainly in the distal ileum and the cecum and those with mainly or solely colonic involvement ($p>0.05$).

The patients were also subdivided into four more distinct anatomical groups (table I). Thus, 14 of the 27 patients with the disease restricted entirely to the distal ileum developed a recurrence, a crude recurrence rate of 52%. This is to compare with 50 patients with the lesions in the distal ileum and the cecum, of whom 18 patients had a recurrence (= crude recurrence rate of 36%). The cumulative recurrence rate was at 15 years 52% and 38%, respectively. This difference was not statistically significant ($p>0.05$).

Location of the disease in the bowel	Number of patients	Pats with recurrence	Crude recur rate %	Cum recur rate at 15 years %	Pats with second resection	Crude rate %	Cum probability of a second resection at 15 years %
Small bowel prox distal ileum	4	2			2		
Distal ileum	27	14	52	52	8	30	31
Distal ileum and cecum	50	32	42	43	8	21	28
Colon and distal ileum	74	41	55	63	34	46	50
Colon only	13	8	62	62	4	31	47
Total	168	83	49	53	56	33	39

Table I: Recurrence rates and cumulative probability of having a second resection in relation to the extent of Crohn's disease in the bowel in patients, subjected to primary radical operation.

$s = \text{Chi-square} = 8.7 \text{ } p < 0.01$

$s^x = \text{---} = 10.7 \text{ } p < 0.01$

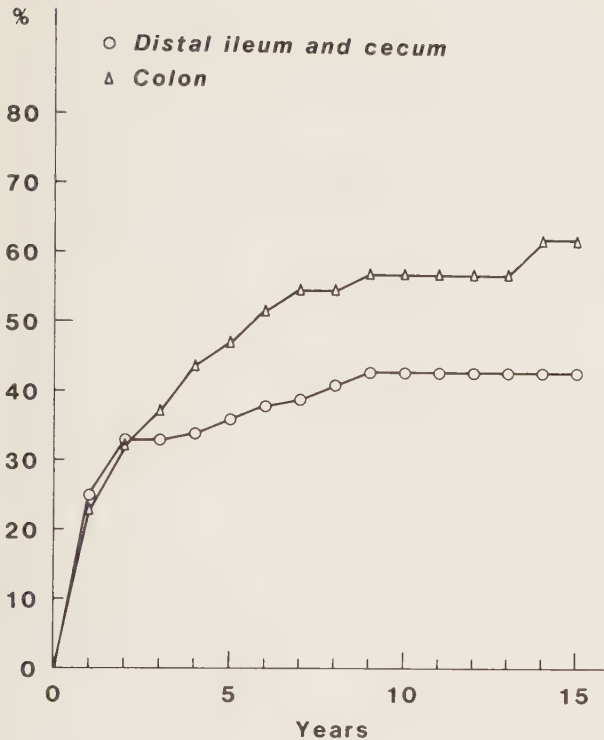


Fig 3: Cumulative recurrence rates after primary "radical" resection for Crohn's disease, in relation to extent of the disease in the bowel.

SE = 2 standard errors of the recurrence rate

$N^{\circ} = 77$ $n^{\circ} = 11$

$N^{\Delta} = 87$ $n^{\Delta} = 9$

Of the 74 patients with mainly colonic Crohn's disease but with involvement of various length of the distal ileum as well, 41 developed a recurrence, a crude recurrence rate of 55%. Eight of the 13 cases with the disease confined to the large intestine had a recurrence (= 62%). The cumulative recurrence rate for these two groups were at 15 years 63% and 62%, respectively. There was no statistically significant difference between the groups ($p > 0.05$).

RECURRENCE RATE IN RELATION TO THE PRIMARY PROCEDURES PERFORMED

As appears from table II resection of the small bowel and anastomosis was performed in five patients, with recurrence in four of them. At the time of the primary operation it was not known that two of these five patients had in fact lesions in the distal ileum as well as in the cecum. Thus, these two patients did not have recurrence but rather relapse of persisting disease.

One hundred and two patients underwent an ileocolic resection and anastomosis and nearly half of them, 49 patients, developed a recurrence, a crude recurrence rate of 48%. The cumulative recurrence rate at 15 years was 52% (fig 4).

Colectomy with ileorectal anastomosis as a primary procedure was performed in ten patients. Recurrent disease in the distal ileum developed in six of them. Another nine patients, initially subjected to colectomy and ileostomy, had later on the continuity of the bowel reestablished as a secondary procedure. Five of these patients had a recurrence. Thus, the crude recurrence rate after colectomy with ileorectal anastomosis was 58% (11/19 patients). The cumulative recurrence rate at 15 years was 59% (fig 4).

Colectomy with a permanent ileostomy was carried out in 31 patients, and recurrent disease in the small bowel occurred in 13 (42%). The cumulative recurrence rate at 15 years was 43% (fig 4).

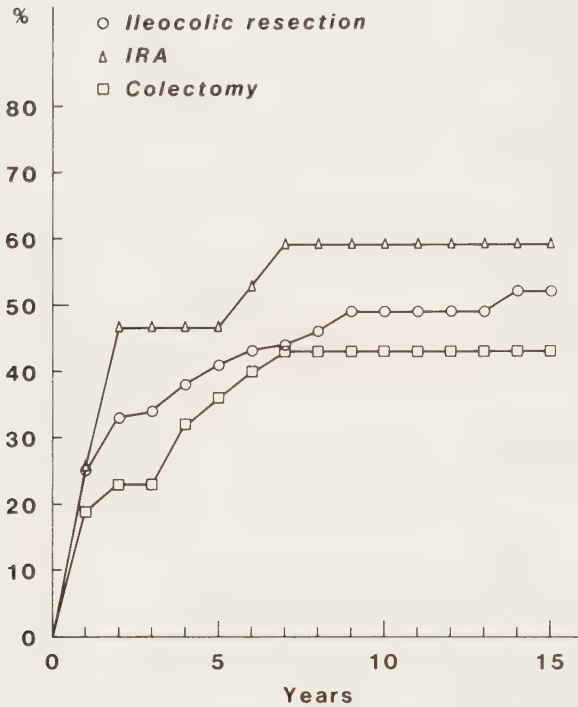
Seven patients underwent proctocolectomy and in four of them the disease recurred.

In three cases an abdominoperineal excision of the rectum as the only primary procedure was carried out, two of them having a recurrence.

Type of operation	No of patients	Pats with recurrence	Crude recur rate	Cum recur rate at 15 years %	Pats with second resection	Crude rate %	Cum probability of a second resection at 15 years %
Small bowel resection	5	4			3		
Ileocolic resection	102	49	48	52	30	29	32
Colectomy, primary IRA	10	6	60	58	3	30	38
Colectomy, secondary IRA	9	5	56	59	4	37	44
Colectomy with ileostomy	31	13	42	43	12	39	45
Proctocolectomy	7	4	57	46	4	42	49
Proctectomy	3	2			0		
Segm colonic resection	1	0					
Total	168	83	49	53	56	33	39

Table II: Recurrence rates and cumulative probability of having a second resection in relation to primary radical procedures in patients with Crohn's disease.

IRA = ileorectal anastomosis



Year	○ %	S.E.	△ %	S.E.	□ %	S.E.
1	25		26		19	
2	33		47		23	
3	34		47		23	
4	38		47		32	
5	41 ± 10		47 ± 23		36 ± 17	
6	43		53		40	
7	44		59		43	
8	46		59		43	
9	49		59		43	
10	49 ± 10		59 ± 23		43 ± 18	
11	49		59		43	
12	49		59		43	
13	49		59		43	
14	52		59		43	
15	52 ± 12		59 ± 23		43 ± 18	

Fig 4: Cumulative recurrence rates after primary "radical" resection for Crohn's disease, in relation to different operative procedures.

SE = 2 standard errors of the recurrence rate

$N^{\circ} = 102$ $n^{\circ} = 15$

$N^{\triangle} = 19$ $n^{\triangle} = 1$

$N^{\square} = 31$ $n^{\square} = 1$

There was no difference in the recurrence rates between patients operated upon with an ileocolic resection and patients who underwent colectomy with ileostomy or ileorectal anastomosis ($p > 0.05$). The number of patients in the remaining groups were too small to allow statistical calculations.

RECURRENCE RATE IN RELATION TO THE HISTOPATHOLOGICAL APPEARANCE OF THE RESECTION MARGINS

The prognostic implication of the histopathological appearance of the resection lines was studied in patients, initially subjected to resection of the bowel with anastomosis. Such an operation was performed in 118 patients. Histological sections from the resection lines were partly or completely missing in eight cases. Thus, there remained 110 patients for this part of the investigation (table III).

At the reexamination the patients were subdivided into three groups, according to the histological appearance of the resection margins. 1/ normal appearance. 2/ major inflammatory lesions, such as ulcers, crypt abscesses and/or giant cell granulomas. 3/ minor lesions, such as increased number of inflammatory cells in the mucosa or the submucosa.

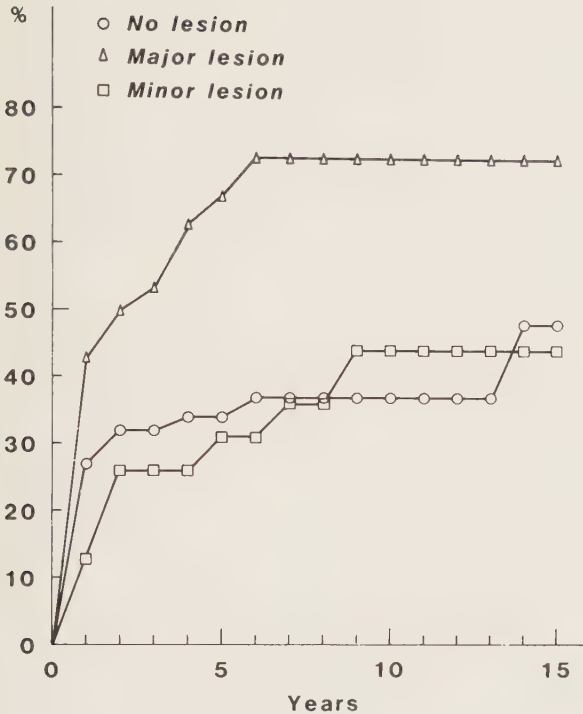
In 41 patients there was no appearance of inflammation in the resection margins microscopically. Sixteen of them developed recurrence (39%). In another 30 patients major lesions in some or in both of the margins were seen, and 22 of these had a recurrence (73%). Sixteen of the remaining 39 patients with only minor inflammatory lesions in the resection lines developed recurrent disease (41%). The cumulative recurrence rates for the three groups were at 15 years 48%, 73% and 44%, respectively (fig 5).

The recurrence rates for the patients without lesions or only minor lesions at the resection margins were significantly lower ($p < 0.01$ and $p < 0.05$, respectively) than the recurrence rate for patients with major lesions when calculating from crude figures. When using the actuarial method there was also a statistically significant difference at ten years between patients without lesions and patients with major lesions, but at 15 years the difference was not significant. Using this

Microscopic appearance	No of patients	Pats with recurrence	Crude recur rate	Cum recur rate at 15 years %	Pats with second resection	Crude rate %	Cum probability of a second resection at 15 years %
No lesions	41	16	39	48	7	17	21
Major lesions	30	22	73	73	16	53	65
Minor lesions	39	16	41	44	10	26	29

Table III: Recurrence rates and cumulative probability of having a second resection after primary radical resection and anastomosis for Crohn's disease, in relation to microscopic appearance of the resection margins.

$ss = \text{Chi-square} = 6.9 \quad p < 0.01$
 $ss^X = - \quad - = 8.8 \quad p < 0.01$
 $s = - \quad - = 5.9 \quad p < 0.05$
 $s^X = - \quad - = 4.4 \quad p < 0.05$



Year	○ % S.E.	△ % S.E.	□ % S.E.
1	27	43	13
2	32	50	26
3	32	53	26
4	34	63	26
5	34 ± 15	67 ± 17	31 ± 15
6	37	73	31
7	37	73	36
8	37	73	36
9	37	73	44
10	37 ± 15	73 ± 16	44 ± 17
11	37	73	44
12	37	73	44
13	37	73	44
14	48	73	44
15	48 ± 24	73 ± 16	44 ± 17

Fig 5: Cumulative recurrence rates after primary "radical" resection and anastomosis for Crohn's disease, in relation to the microscopical appearance of the resection margins.

SE = 2 standard errors of the recurrence rate

$N^{\circ} = 41$ $n^{\circ} = 6$

$N^{\Delta} = 30$ $n^{\Delta} = 1$

$N^{\square} = 39$ $n^{\square} = 6$

method, no significant difference was found between patients with minor lesions and those with major lesions.

The presented analysis of the resection lines was performed irrespective of the extent of the disease in the bowel. Therefore, available slides from histological sections from the margins in 69 patients with a more limited extent of the

disease, i.e. the distal ileum and cecum, operated upon with an ileocolic resection, were examined (table IV). Of 36 patients

Microscopic appearance	No of patients	Pats with recur	Crude rate %	Second resection	Crude rate %
No lesions	36	12	33	5	14
Major lesions	8	6	75	4	50
Minor lesions	25	9	36	6	24
Total	69	27	39	15	22

Table IV: Recurrence rates and numbers of patients with a second resection after primary radical ileocolic resection for Crohn's disease in patients with the disease confined to distal ileum and cecum, in relation to the microscopic appearance of the resection margins.

without lesions 12 developed a recurrence (33%). Major lesions in some of the margins were seen in eight patients and six of them had a recurrence. Nine of the remaining 25 cases with minor lesions developed recurrent disease (36%). The number of patients with major lesions was too small to allow statistical analysis, therefore no cumulative rates were calculated for any of the three groups.

RISK OF HAVING A SECOND RESECTION FOR RECURRENCE

1. Patients with recurrence, not reoperated upon.

After the initial operation 83 patients developed recurrent disease. However, 12 of these patients had no symptoms at all though the recurrences were diagnosed on repeated radiological

examinations. They were not reoperated upon. Another nine patients were not reoperated upon either, six of them having only minor symptoms, and three patients having disseminated lesions in the intestine, as seen radiologically.

II. Patients with recurrence, reoperated upon

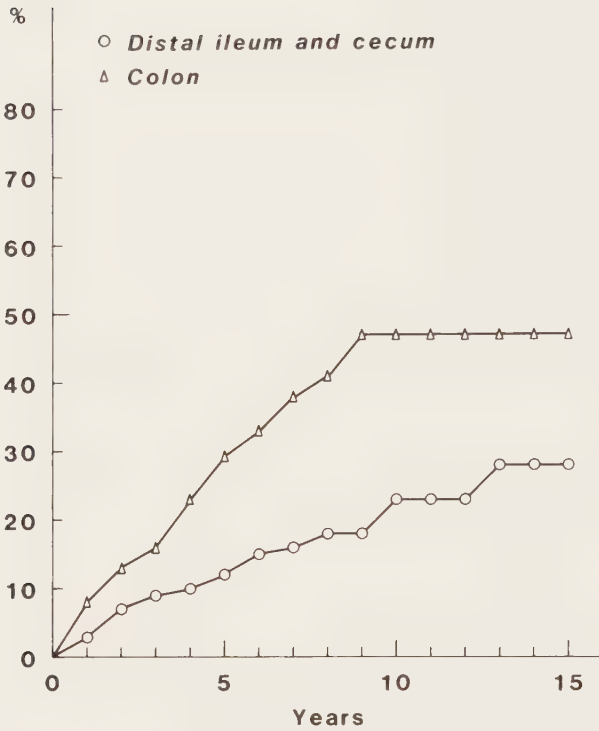
Sixty-two patients were subjected to a second operation due to recurrence (62/168 patients = 37%). In three of these patients, reoperated upon, only a diverting ileostomy without resection was performed and in another two patients explorative laparotomy only. One patient had an ileotransversostomy without exclusion. In the remaining 56 patients a second resection was carried out and the calculated risk of having another resection was based on this group of patients.

a. In relation to the extent of the disease

Sixteen of the 77 patients with Crohn's disease predominantly confined to the small bowel underwent a second resection (21%). The cumulative probability of having another resection was 28% at 15 years (table I). The corresponding figures for the patients with mainly or solely colonic disease were: crude rate 44% (38/87 patients), cumulative probability at 15 years 47%. When calculated from crude figures there was a difference between the groups in favour of patients with predominantly small bowel involvement ($p < 0.01$). When calculated according to the actuarial method there was a difference at ten years but not at 15 years (fig 6).

b. In relation to primary operations performed

Thirty of the 102 patients, 29%, subjected to an ileocolic resection, were re-resected, while seven of the 19 patients (37%) operated upon with an ileorectal anastomosis had to have a resection of the new distal ileum and an ileostomy (table II). Sixteen of the 38 patients (42%), who had a colectomy or proctocolectomy with a permanent ileostomy, needed a second resection.



Year	○		△	
	%	S.E.	%	S.E.
1	3		8	
2	7		13	
3	9		16	
4	10		23	
5	12 ± 7		29 ± 10	
6	15		33	
7	16		38	
8	18		41	
9	18		47	
10	23 ± 11		47 ± 12	
11	23		47	
12	23		47	
13	28		47	
14	28		47	
15	28 ± 14		47 ± 12	

Fig 6: Cumulative probability of having a second resection after primary "radical" resection for Crohn's disease, in relation to extent of the disease in the bowel.

SE = 2 standard errors of the recurrence rate

$N^{\circ} = 77$

$n^{\circ} = 14$

$N^{\Delta} = 87$

$n^{\Delta} = 11$

The cumulative probability of having a second resection was at 15 years 32%, 38% and 49%, respectively. There was no statistically significant difference between the three groups ($p > 0.05$).

c. In relation to the resection margins

As seen in table III, seven of the 41 patients (17%) without lesions in the resection lines had a second resection, and the cumulative probability at 15 years was 21%. The correspon-

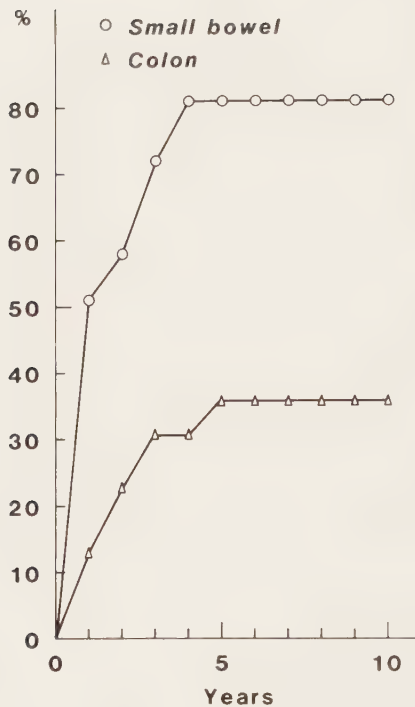
ding figures for patients with minor lesions were almost the same, while 53% (16/30 patients) of the patients with major lesions had to have a second resection. The cumulative probability for this latter group was 65%. There was a statistically significant difference, when calculated from crude figures, between patients without lesions or only minor lesions and the patients with major lesions ($p < 0.01$ and $p < 0.05$, respectively). When computed according to the actuarial method there was a difference between patients without lesions and patients with major lesions, both at ten and 15 years ($p < 0.05$).

Concerning the patients with a more limited extension of the disease (table IV) the crude rates of having a second resection were similar to the above mentioned figures.

RECURRENCE RATE AFTER SECOND RADICAL RESECTION

As mentioned above a second resection due to recurrent disease was performed in 56 patients. In five of these cases the resection was palliative while in the remaining 51 patients the resection was "radical". Recurrence after this second "radical" resection was seen in 13 of the 18 patients (72%) with the disease confined to the distal ileum and the cecum, while 11 of the 33 patients (33%) with the disease predominantly or exclusively confined to the large bowel developed recurrence. The cumulative recurrence rates at ten years were 81% and 36%, respectively (fig 7). The difference was statistically significant ($p < 0.05$).

Ten of the 24 patients with a recurrence had a third resection (42%). The cumulative probability of having a second resection was not calculated due to the small numbers of patients.



Year	○ %	S.E.	△ %	S.E.
1	52		13	
2	58		23	
3	72		31	
4	81		31	
5	81 ± 22		36 ± 19	
6	81		36	
7	81		36	
8	81		36	
9	81		36	
10	81 ± 22		36 ± 19	

Fig 7: Cumulative recurrence rates after second "radical" resection for Crohn's disease, in relation to extent of the disease in the bowel.

SE = 2 standard errors of the recurrence rate

$N^{\circ} = 18$ $n^{\circ} = 1$

$N^{\Delta} = 33$ $n^{\Delta} = 6$

DISCUSSION

Many studies concerning the recurrence rate after surgical treatment of Crohn's disease have been published throughout the years. One of the difficulties in comparing different studies is the use of various criteria for recurrence. The definition used in the present study - "the Cape Town classification" - is described by Lee & Papaioannou (17).

It includes patients reoperated upon due to recurrence and patients with objective signs of recurrence but not reoperated upon or without clinical symptoms, while patients with symptoms such as diarrhoea or weight loss as the only signs of a possible recurrence will be excluded. As pointed out by Lennard-Jones & Stalder (8) such symptoms could result from the surgery employed and do not necessarily reflect a true recurrence.

Lennard-Jones & Stalder (8) in their discussion of various definitions of recurrence pointed out that there are two other possibilities to define recurrence besides symptoms only. Recurrence could be symptomatic and the diagnosis supported by radiographical examination and/or verified by surgery. This definition will lead to an underestimation as there are patients with radiographical evidence of recurrence but without any symptoms at all. This has also been stressed by others. A third possibility of defining recurrence is further resection of the bowel. This definition will also give a too low recurrence rate since not every patient with clear symptoms and radiographical evidences of recurrence will need a reoperation.

Another problem concerns the way the recurrence rates are calculated. Using crude figures only is considered to underestimate the recurrence rate (4,8-13). The reason for this is that there has been no correction for the shorter observation time in patients operated upon at the end of the investigation period. Statistical analysis according to the actuarial method as described by Hill in 1966 (14) and first used in a study of Crohn's disease by Lennard-Jones & Stalder in 1967 (8) takes this problem into consideration. During the last decade it has been common to report recurrence rate calculated according to this method in order to facilitate comparisons between different studies. In general, the cumulative rates have been on a higher level than the crude rates, and in some reports the discrepancy

has been large (7,9,10). In the present study no great difference was found, the cumulative rates exceeded the crude rates with only a few percent, a finding which has also been reported by Hellberg (12). The probable explanation is that the longer the observation time the better the agreement between observed and estimated rates. Thus, a more reliable comparison of recurrence rates in various series with short observation time is possible, when the life table method is used. It must be remembered, however, that this is only valid if the follow-up protocol and definitions have been reasonable similar in the series compared.

In the present series the patients were clinically and radiographically examined on repeated occasions during the first postoperative years. Most of the recurrences were traced early, a fact which is apparent from the cumulative curves. The first technically satisfactory radiographical examination were also found to be of great prognostic importance. All but five of 86 patients, in whom the first postoperative small bowel radiography was normal, have remained disease-free during the follow-up period. Thus, if the first postoperative radiological examination of the small bowel is normal, the risk of having a recurrence within a mean observation time of ten years is less than six percent.

In the present series it was found that age at the time of operation had no implication on the recurrence rate. This finding was in accordance with others' reported (4,8,12,13,24-26). However, Stahlgren & Ferguson, Atwell, Duthie & Goligher, de Dombal, Burton & Goligher, Steinberg et al, Hellers and Cooke et al (7,11,16,27-29) have reported that younger patients were more prone to develop recurrence than older patients.

The length of the disease history prior to operation had no influence on the recurrence rate, and the same findings have

been reported by others (11,12,24-26,28). Schofield (30) and Steinberg et al (7) have reported that patients with a short history were more susceptible to recurrence than patients with a longer duration of the disease.

It is a widely held opinion that the distribution of the disease in the bowel is of great importance concerning the clinical course of the disease and the recurrence rate (12,13, 29,31). In the present study no difference in recurrence rates between any of the different extents of the disease was found. Patients with the disease confined to the terminal ileum and the cecum showed a tendency to a somewhat lower recurrence rate than the patients with ileocolitis. However, this difference was not statistically significant. Others have reported that the rate of recurrent disease for patients with mainly small bowel involvement was higher than for patients with predominantly or exclusively colonic disease (11,29,32). The highest rates have been found when both small and large intestine were involved (13,24,33) while the propensity to recurrence in patients with exclusively colonic disease was lower.

When radical procedures are performed the operations largely reflect the site of the disease. The recurrence rate after ileocolic resection was similar to that of the total series, a fact that can easily be understood as this type of operation represented more than 60% of all procedures performed.

The recurrence rate for patients operated upon with colectomy and ileorectal anastomosis, either as a one-stage or two-stage procedure, was in agreement with those reported by Nugent et al, Burman, Cooke & Alexander-Williams, Goligher and Buchmann et al (1,34-36). Weterman & Pena in 1976 (37) even found that 3/4 of the patients developed recurrent disease. In other studies the recurrence rate has been found to be somewhat lower (12,38-42). An analysis of the risk of recurrence

after this type of operation in the present series will be published in a forthcoming report (IV).

The recurrence rate after colectomy with a permanent ileostomy and proctocolectomy in the present study was about 50%, both when calculated with the crude figures and according to the actuarial method. Earlier the crude recurrence rate after these procedures has been reported by several authors to be low (1,2,29,35,40). However, when the actuarial method has been used, the rates have increased and in 1974 Steinberg et al (7) found that all patients developed recurrent disease within 18 years.

The policy in the present study concerning the resection of the bowel was that all grossly involved intestinal tissue should be removed, if possible. Therefore, the specimens were per-operatively opened and examined and, if lesions were detected near the resection margin, a further resection was carried out. Such a procedure has also been recommended by others, for example Atwell, Duthie & Goligher, Krause, Bergman & Norlén and Hellberg et al (12,24,28). In the two latter studies a resection of macroscopically healthy intestine about 10 - 20 cm on the proximal side of the involved bowel was performed, and this was also carried out in most patients in the present study. The microscopic appearance of the resection margins, on the other hand, was not known until later on postoperatively. Examination of frozen-sections of the margins, a technique advocated by Kåresen et al, Hellberg et al and Mühe et al (12,43,44) was not considered to give adequate information and this technique was not used.

The significance of the histological appearance of the resection margins when calculating the recurrence rates has been reported on in only a few previous papers (17,43,45). Pennington et al in 1980 (45) examined 100 patients, on whom resection

with anastomosis had been carried out. They found that it was of no account whether the resection lines were healthy or showed inflammatory lesions. The same result was found by Lee & Papaioannou (17). In the present study, however, a statistically significant difference was seen between patients with no lesions or only minor inflammatory lesions and patients showing major lesions, such as ulcers, crypt abscesses or giant cell granuloma , and this has also been reported by Kåresen et al (43). In the present study there was a significant difference after ten years but not at 15 years. The reason for this latter finding may be that the number of patients was too small at 15 years.

There has been some controversy in the literature as to the risk of having a second operation due to recurrent disease after primary resection. In the present study, between 30% and 50% of the patients with evidence of recurrence needed a second resection, and this finding was in accordance with others (4,5,8,12,28). Greenstein et al (9) included all types of major surgical treatment, including by-pass procedures and drainage of intraabdominal abscesses, when defining recurrence. They also reported a higher frequency of reoperations, about 90%. A similar high rate was found in the NCCDS study (46) and in the study by HELLERS in 1979 (11) and in this latter report resections only as the secondary procedure were included.

When the second resection rate was correlated to different extents of the disease there was a statistically significant difference between patients with predominantly small bowel disease and patients with mainly or exclusively colonic involvement. In a study from Gothenburg in 1980 (12) no difference between the two groups of patients was reported, provided the diagnosis in cases with a colonic Crohn's disease was certain and cases with indeterminate colitis were excluded. In that study all patients with predominantly large bowel disease and

recurrence required a re-resection while in the present study almost 1/4 of the cases did not undergo a second resection. Concerning patients with small bowel disease there was no difference between the two studies, about 50% of the patients with recurrence had to have a second resection, due to aggravation of symptoms.

When calculating the cumulative probability of having a second resection the curves have a somewhat different course than the cumulative recurrence curves. This difference is due to the fact that not all patients with recurrent disease needed another resection and that patients with radiological evidence of recurrence, detected early during the follow-up period, may not have subjective symptoms until later on (so called "radiological recurrences").

The overall recurrence rate in the present study was in accordance with that of the majority of earlier published series about the outcome after resectional therapy for Crohn's disease. It is obvious that about 50% of the patients, irrespective of type of extension, will develop recurrent disease, and that 25-30% need a second resection.

Electronic microscopical examinations of microscopically uninvolved bowel and other examinations of grossly uninvolved intestinal segments in patients, suffering from Crohn's disease have revealed abnormalities that are not seen in control patients (47,48). These findings support the view that Crohn's disease may involve the whole intestine and helps to explain why patients on whom "radical" resections have been performed still may develop recurrent disease. The term "recurrence" is thus not quite appropriate even if widely used. Maybe "relapse" is a better designation. It is true that extirpation by resection is not a definite guarantee against progress of the disease, but there is no evidence that this procedure will

promote spread of the disease, as proposed by Mendeloff in 1975 (49). On the contrary, it can be agreed with Glotzer (50) who stated that "among the therapies available, operation is unique in that it may offer the potential for cure", even if reservations must be made for possible recurrences occurring after longer postoperative time than has been possible to study in this and other series.

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II

EARLY SURGERY FOR CROHN'S DISEASE

by

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ABSTRACT

In an analysis of a consecutive series of 133 patients with the diagnosis of Crohn's disease established preoperatively and where early surgical intervention was the prevailing policy, it was found that the median time between diagnosis and operation was short. In patients with predominantly small bowel disease it was four months, in patients with predominantly colonic involvement eight months. The frequencies of preoperative and early postoperative complications were low, compared to those in other reports. Local complications, such as intraabdominal fistulae and abscesses, were preoperatively seen in only four per cent of the patients. Arthritis, iritis or erythema nodosum were not seen in patients with predominantly small bowel disease. Recurrent disease was seen in 53% of 123 patients, "radically" resected. Early postoperative death rate was 1.5%, late mortality rate 3%. It is concluded that the risk of developing preoperative as well as early postoperative complications will diminish, if early surgery is performed.

INTRODUCTION

Opinions differ whether patients with Crohn's disease should be treated conservatively as long as possible or be operated upon early, in order to avoid serious complications. The aim of the present investigation was to analyse local and systemic pre- and postoperative complications in relation to the length of the preoperative interval in a series of patients with preoperatively diagnosed Crohn's disease in the city of Malmö, Sweden, concecutively operated upon during the years 1958 through 1974. It was also aimed to compare the results with those in other reports in order to evaluate the effect of early surgery on the rate of complications and of recurrence.

PATIENTS AND METHODS

All patients diagnosed as having Crohn's disease in the defined population of Malmö, Sweden, during the years 1958 through 1973 were traced by Brahme et al (1) in an epidemiological survey. With the addition of the corresponding patients from the following year and after reexamination, as described below, 207 patients altogether were found to have Crohn's disease diagnosed during 1958 through 1974 (table I).

From the total series, 49 patients were excluded, in whom the diagnosis was not established preoperatively. The indications for surgery in these 49 patients are listed in table II. Another 12 patients, with the disease confined to the appendix vermiformis, were also excluded. These 61 patients are discussed in forthcoming reports (I, III, IV, V).

In addition 13 patients, not operated upon during the investigation period, were excluded. The outcome for these 13 patients after 1974 were the following: Two patients had proctocolectomy and one patient colectomy with ileorectal anastomosis performed.

The diagnosis in the cases not resected was established by histopathological analysis of biopsies during explorative laparotomy or from the rectum and by radiography in seven cases. In three cases the diagnosis was only based on radiography. Four of the ten non-resected patients with disseminated lesions in the small bowel were on treatment with drugs, such as corticosteroids, sulphasalazine (Salazopyrine^R) and azathioprine (Imurel^R). Another patient, with lesions confined to the distal ileum, refused an operation. In three patients, with typical radiographical signs of Crohn's ileocolitis, the disease showed clinical and radiological regression. These three patients were doing perfectly well at the latest clinical check-up. The remaining two patients were lost to follow-up.

	C.D.: Diagnosis established preoperatively No of patients	C.D.: Diagnosis not established preoperatively No of patients	Total numbers of patients
Resection	133	49	182
Appendicec- tomy only		12	12
Diagnosed but not operated upon			13
			207

Table I: Patients with Crohn's disease (C.D.)
in Malmö 1958 - 1974

	Predomi- nantly small bowel disease	Predomi- nantly large bowel disease	Total number of patients
Ulcerative colitis	-	15	15
Suspicion of appen- dicitis	9	2	11
Intestinal obstruc- tion	8	-	8
Suspicion of malig- nancy	4	2	6
Suspicion of gyne- cological disease	3	-	3
Suspicion of appen- diceal abscess	2	-	2
Intestinal hemorr- hage	-	1	1
Polyposis coli	-	1	1
Abdominal mass	-	1	1
Partial obstruction of the small bowel	1	-	1
			49

Table II: Indications for surgery in patients with Crohn's disease, in whom the diagnosis was unknown at the time of the primary operation.

Thus, the series for study included 133 patients, 53 males and 80 females. The age of the patients at the time of the primary operative procedure ranged from 10 to 75 years with a median of 22 years (mean 26 years).

The policy was to open the specimens during the operation and examine them in order to avoid resection in grossly diseased bowel. In several cases with colectomy and ileostomy a diseased rectum was left for a possible ileorectal anastomosis later on. After preparation the specimens were measured and macrophotographed and then fixed in 10% formalin solution on large specially made trays to preserve good morphology. After fixation a large number of histological sections from the bowel and lymph-nodes were prepared and examined.

All patients were postoperatively checked-up at Malmö General Hospital, but 22 patients later on moved out from the city and were thereafter mainly examined elsewhere. The results of these examinations were included in this analysis.

At the end of the follow-up period, December 31st 1979, the median time between the primary procedure and the latest clinical examination or the date of death was 8.8 years (mean 9.4 years, range 1.5 - 19.7 years).

Since all case records, radiograms, histopathological sections from biopsies or specimens have been kept (since 1969, the whole specimens) it was possible to perform a thorough reexamination of all available data including case histories, operative findings etc. This reevaluation was performed by the authors, i.e. four surgeons, one radiologist (JH) and one pathologist (CL).

In all cases the diagnosis was based on histopathological examinations of surgical specimens using the criteria reported by Lockhart-Mummery & Morson (2) and Price & Morson (3).

The radiographical criteria used were those reported by Laufer (4), Sellink (5) and Hildell (6).

The extent of the lesions in the bowel, as assessed at the re-evaluation, is seen in fig 1.

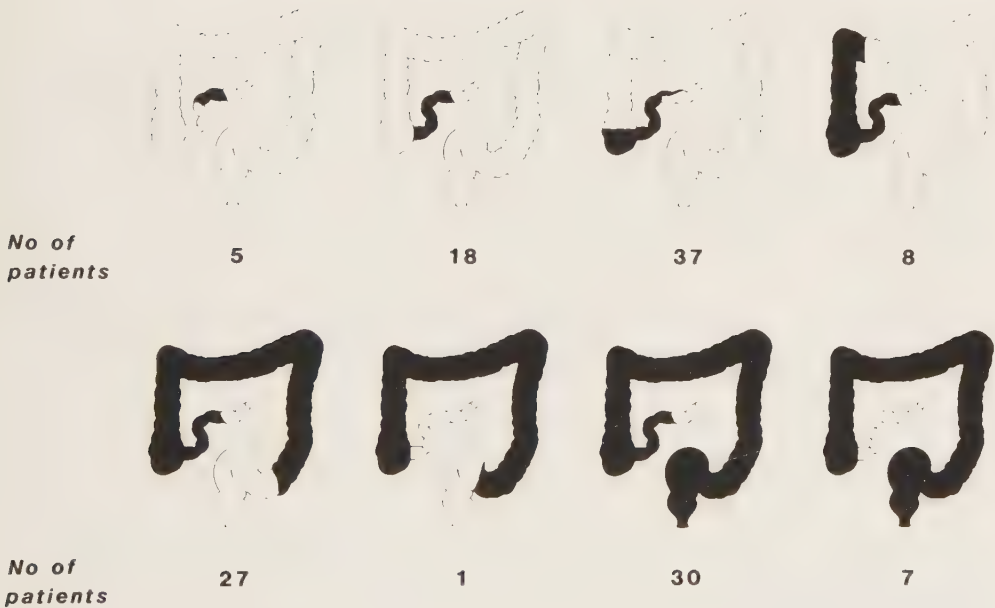


Figure 1: Extent of Crohn's disease in the bowel at the time of the primary operation in patients with diagnosis established preoperatively

In 60 patients the disease was confined to the small bowel with co-existing lesions in the cecum in 37 cases (predominantly small bowel disease). The remaining 73 patients had the disease predominantly in the large bowel and most of them, 65 patients, with ileal involvement.

Recurrent disease was defined according to the "Cape Town Classification (7): with recurrence is meant the appearance of objective signs - defined radiologically, endoscopically or histopathologically - of Crohn's disease in the bowel of a patient who has previously had resection of all macroscopically diseased tissue".

Recurrence rates were calculated both with crude figures and according to the actuarial method (8, 9). Differences between crude recurrence figures were calculated using Chi square test. When calculating the cumulative recurrence rates, according to the actuarial method, a computer was used. Significance level considered was 5% ($p < 0.05$).

As assessed at the reevaluation, the patients were divided into three groups, according to the degree of general health - "quality of life" - at the latest clinical check-up, which in all surviving patients was performed during the second half of 1978 or during 1979. The definitions of the groups were:

Quality of life I: The patient was in a good general state of health, able to do full time work and to have normal leisure time activities.

Quality of life II: The patient was able to work part time and the leisure time activities were restricted due to diarrhoea, pain etc.

Quality of life III: The patient could not work at all and the leisure time activities were severely restricted by for

example frequent diarrhoea, general weakness or pain.

RESULTS

DURATION OF THE PREOPERATIVE DISEASE HISTORY

The median time between *onset* of subjective symptoms and *diagnosis* for patients with predominantly small bowel disease was five months, and the mean 16 months (range 1 month - 12 years). The corresponding figures for patients with mainly colonic involvement were: median 5 months and mean 11 months (range 0 - 5.8 years).

The time between *diagnosis* and *primary operation* in patients with predominantly small bowel disease was: median 4 months, mean 12 months (range 1 month - 7.7 years). Predominantly colonic disease was: median 8 months, mean 18 months (range 1 month - 12 years). Thus, the disease history from the diagnosis until operation was longer for patients with Crohn's disease predominantly located to the large bowel.

FREQUENCY OF PREOPERATIVE COMPLICATIONS

Systemic and local complications occurring during the preoperative period and the time of development after subjective onset of the disease are listed in table III.

Systemic complications

The most common but less serious complication was erythema nodosum, observed in 14 patients. Arthritis, defined as attacks of painful distended joint, as well as episcleritis, was seen when the disease was in an active phase and occurred only in patients with predominantly large bowel disease. In the patients with amenorrhea during disease the menstruation returned to normal after the operation or when the disease was inactive.

Complications	At onset	1 - 5	6 - 11	12 - 23	≥ 24 months	Total no of patients	Percentage of total no of patients	Total %
<u>Systemic</u>								
Arthritis	0 + 4	0 + 1	0 + 2	0 + 1	0 + 2	10	0 + 14	8
Episcleritis/iritis			0 + 1		0 + 1	2	0 + 3	2
Erythema nodosum	1 + 4	0 + 1		1 + 0	0 + 7	14	3 + 16	11
Amenorrhea	1 + 2	1 + 1	1 + 0	1 + 0		7	-	-
Biliary stones	1 + 1	1 + 0		0 + 1	1 + 1	6	5 + 4	5
Urinary stones		0 + 1			0 + 2	3	0 + 4	2
Duodenal ulcer		1 + 1			1 + 2	5	3 + 4	4
Stunted growth/ sexual development						7	-	-
<u>Local</u>								
Anal fistula	1 + 5	0 + 5	2 + 2	1 + 2	2 + 10	30	10 + 33	23
Entero-cutaneous fistulae/abscess		6 + 1				7	10 + 1	5
Intraabdominal fistulae/abscess		0 + 1		0 + 1	0 + 3	5	0 + 7	4
Recto-vaginal fistula					0 + 1	1	0 + 1	1
Intestinal hemorrhage	0 + 1	0 + 3		0 + 2	2 + 6	14	3 + 16	11

Table III: Preoperative systemic and Local complications in relation to time of occurrence in patients with preoperatively known Crohn's disease.

Figures to the left represent patients with small bowel involvement, and to the right patients with mainly or exclusively large bowel disease

Retarded growth and stunting of sexual development occurred in seven patients. In two of them the time interval between diagnosis and operation was long, 4.6 and 6.3 years, respectively.

Local complications

Anal fistulae

The most common preoperative complication was anal fistulae, occurring in six of the patients with predominantly small bowel disease (6/60 patients = 10%) and in 24 of those with mainly colonic involvement (24/73 patients = 33%). In six of the patients the anal fistulae were noted at the onset while in another 15 patients this complication occurred after more than one year's disease. In 18 cases the fistulae were excised before the major intestinal operation and then with a successful result in 13. In four of the remaining five patients the fistula was successfully excised postoperatively, while the fistula in the fifth patient did not heal and the patient eventually underwent proctectomy.

Of the 12 patients, not operated upon preoperatively for this complication, the fistulae healed spontaneously in four cases, in one of them before the major procedure and in the other three after the primary intestinal resection. Another six patients were successfully treated with excision of the anal fistula after the primary procedure. In one of the remaining two patients the major procedure was proctocolectomy, while the other patient subsequently underwent proctectomy.

Entero-cutaneous fistulae/abscesses

A fistula between the involved cecum and the abdominal wall occurred in the post-appendicectomy period in three of 16 patients, in whom the disease was diagnosed at laparotomy performed due to the suspicion of appendicitis or appendiceal abscess before the major operation. Another of the 16 patients developed an abscess in the abdominal wall.

In another two patients such fistulae occurred after drainage of a cecal abscess, while in one additional patient the abscess involved the abdominal wall as well. The fistulae/abscesses did not heal until the diseased segment of the bowel was resected.

Intraabdominal fistulae/abscesses

A fistula between distal ileum and sigmoid colon was seen preoperatively on radiograms in two patients, one of them having a recto-vaginal fistula as well. These complications developed two and four years after the onset, respectively.

One patient developed an abscess around the cecum after 20 months' disease.

In another two patients small sinuses from the sigmoid colon were seen on radiograms.

Intestinal hemorrhage

Significant intestinal bleeding, requiring transfusion, occurred in two patients with mainly small bowel disease (2/60 patients = 3%), three and five years after onset, respectively. Concerning patients with predominantly colonic involvement this complication occurred in 12/73 patients (16%). In one of the patients the hemorrhage was the first sign of the disease, while in eight cases this complication occurred after more than one year's disease history (range 14 months - 7 years). In the remaining three cases the hemorrhage was seen during the first months of the disease history.

PREOPERATIVE TREATMENT

The majority of the patients (78/133 patients) were treated with corticosteroids or sulphasalazine (Salazopyrine^R) or a combination of these drugs for periods of various length. Three patients were treated with azathioprine (Imurel^R), two of them in combination with corticosteroids.

INDICATIONS FOR SURGERY

The indications for surgery are listed in table IV, from which is seen that most of the patients (93 patients) were operated upon due to weight loss, pain and/or diarrhoea. In seven of these patients the primary procedure was an urgent one, due to a rapid deterioration. Another 14 patients, with objective signs of the disease, as shown by radiography, endoscopy and/or blood chemistry, were operated upon though they had only minor symptoms. Anal fistulae that did not heal on conservative treatment indicated surgery in ten cases. Retardation of growth and stunting of sexual development were the main indications in five patients, while the presence of entero-cutaneous fistulae after previously performed appendicectomy or drainage of abscesses were the indications in another seven patients. One patient suffered from an intraabdominal abscess, and one patient had an urgent operation due to intestinal obstruction.

Two patients, with a disease history of three and seven months, respectively, developed fulminant colitis with dilatation of the large bowel and underwent an urgent colectomy with ileostomy.

PRIMARY OPERATIVE PROCEDURES

The primary procedures performed are seen in table V. This table shows, that nearly 2/3 of the patients were operated upon with an ileocecal resection/right hemicolectomy (79 patients). The second main operative procedure was colectomy with ileostomy (37 patients), leaving the rectum for a possible ileorectal anastomosis as a secondary procedure. Colectomy and ileorectal anastomosis as a one-stage procedure was performed in eight patients.

In 125 patients all macroscopically involved intestinal tissue, with the exception of the rectum in some cases, was resected ("radical" resections). In eight patients only part of the

Indication	Predomi- nantly small bowel disease	Predomi- nantly large bowel disease	Total number of patients	Percentage of total number of patients %
Weight loss, pain diarrhoea	39	54	93	70
Minor symptoms	9	5	14	11
Anal fistula	4	6	10	8
Stunted growth/ sexual development	2	3	5	-
Entero-cutaneous fistula	6	1	7	5
Intraabdominal abscess	-	1	1	1
Fulminant colitis	-	2	2	2
Intestinal obstruction	-	1	1	1
	60	73	133	-

Table IV: Indications for surgery in patients with preoperatively known Crohn's disease.

diseased bowel was resected.

EARLY POSTOPERATIVE COMPLICATIONS

Complications during the first postoperative month after the primary resection were recorded in 24 patients (table VI).

Dehiscence of the anastomosis occurred in two patients, and these two patients died in sequelae of this complication. Ten patients were reoperated upon due to *intestinal obstruction* and one of

them soon thereafter developed an *intraabdominal abscess* with fistulae from the small bowel and the rectum, which required repeated reoperations. Intraabdominal abscess was seen in another two patients. In one of these patients the abscess was surgically drained while the other was treated with antibiotics.

Primary procedure	Predominantly small bowel disease	Predominantly large bowel disease	Total number of patients
Small bowel resection	3	1	4
Ileocecal resection/ right hemicolectomy	57	22	79
Ileocecal resection + ileostomy/colostomy		3	3
Colectomy + ileostomy		37	37
Colectomy + IRA		8	8
Proctocolectomy		1	1
Proctectomy		1	1
	60	73	133

Table V: Primary operations performed in patients with preoperatively known Crohn's disease.
IRA = ileorectal anastomosis.

Complications	Predomi- nantly small bowel disease	Predomi- nantly large bowel disease	Total number of pati- ents	Percentage of total number of pati- ents %
Anastomotic dehiscence	1	1	2	1,5
Intestinal obstruction	2	8	10	8
Intraabdominal abscess	2	1	3	2
Entero-cutaneous fistula	1	-	1	1
Wound infection	2	6	8	6
Ileostomy retraction	-	1	1	1

Table VI: Complications occurring in the early postoperative period after primary operation for Crohn's disease.

An *entero-cutaneous fistula* occurred in one patient and this complication was the indication for an early reoperation.

Wound infection, defined as discharge of pus either spontaneous-ly or after the opening of the abdominal wound, was seen in eight patients.

One patient was reoperated upon due to *retraction of the ileostomy*.

RECURRENCE

In 125 of the 133 patients a "radical" resection was performed, while the remaining eight patients had a palliative procedure. During the follow-up period, 58 of the 123 patients (47%), surviving the primary "radical" operation, were apparently free from the disease. Recurrence was seen in 65 patients (53%) and the cumulative recurrence rate at ten years was 54% (table VII). Eleven of these 25 patients had only radiographical evidence of recurrent disease. Fortytwo patients underwent a second resection for recurrence, while in another five patients only ileostomy or explorative laparotomy was performed. The remaining seven patients were conservatively treated for their recurrence.

Fortysix per cent of the patients with predominantly small bowel disease developed recurrence (26/57 patients) while the corresponding figure for the patients with predominantly large bowel disease was 59% (39/66 patients). The difference was not significant ($p>0.05$). The cumulative recurrence rates at ten years were 48% and 60%, respectively. Nine of the eleven patients with so called "radiological recurrence" belonged to the group of predominantly small bowel disease.

Thirteen of the 57 patients (23%) with predominantly small bowel disease required a second resection for recurrence, while such operation was performed in 29 of the 66 patients with predominantly large bowel disease (44%). The difference was statistically significant ($p<0.05$).

LATE POSTOPERATIVE COMPLICATIONS

The complications occurring in the late postoperative period are seen in table VIII. Reoperation due to *intestinal obstruction* was performed 27 times in 19 patients. One of the patients was operated upon five times, another patient three times and two patients twice.

Extent of disease	Number of patients	Number of recurrence	Crude recurrence rate %	Cumulative recurrence rate at 10 years %	Second resection	Crude rate %
Predominantly small bowel disease	57	26	47	48	13	23
Predominantly large bowel disease	66	39	59	60	29	44
	123	65	53	54	42	34

Table VII: Crude and cumulative recurrence rates and crude rate of a second resection for recurrence in relation to extent of the disease in the bowel in patients with preoperatively known Crohn's disease, subjected to a primary "radical" resection.

$$S = \chi^2 = 5,2 \quad p < 0.05$$

Complication	Predominantly small bowel disease	Predominantly large bowel disease	Total number of patients n = 131	Percentage of total number of patients %
Intestinal obstruction	7	12	19	15
Stitch abscess	6	13	19	15
Anal fistula	2	13	15	12
Urinary stones	7	7	14	11
Biliary stones	3	1	4	3
Abdominal hernia	-	4	4	3
Duodenal ulcer	1	3	4	3
Ileostomy problem		15/41	15/41	37
Delayed perineal healing after proctectomy		12/21	12/21	57

Table VIII: Complications occurring in the late postoperative period in patients with Crohn's disease.

Fifteen patients developed *new anal fistulae*. In eight of them this complication occurred at the time of recurrent disease in the bowel. In another six patients, without signs of recurrence, the fistulae were successfully excised but three of these patients later on developed recurrent disease in the intestine. The remaining patient, subjected to a palliative intestinal resection, had an excisional treatment of the new fistula and the outcome of that operation was good.

Ileostomy problems. Retraction of the ileostomy occurred in 11 patients and altogether 18 operations were performed to correct this complication. Another four patients had to get a new ileostomy due to fistulae.

Delayed perineal healing. Proctectomy was performed in 21 cases, and in 12 of them the healing of the perineal wound was delayed by more than three months. The median time for healing was 13 months (mean 22 months, range 3 months - 7 years).

Malignancy. None of the patients developed adeno-carcinoma of the bowel.

MORTALITY

During the follow-up period altogether eight patients died. Two of them (1.5%) died in the first postoperative month after the primary operation. Another two patients died in the early postoperative period after reoperation. The remaining four patients died later on, due to intercurrent diseases, one of them with Crohn-lesions in the bowel as seen at the autopsy. Thus, the late mortality rate was 2.3%.

COMPLICATIONS AFTER REOPERATION

The complications occurring early after 140 different major reoperations are listed in table IX. These major reoperations included reoperations for recurrence, operations for intesti-

Complications	Predominantly small bowel disease	Predominantly large bowel disease	Total number of patients n = 131	Percentage of total number of patients
Intestinal obstruction	-	2	2	2
Intraabdominal hemorrhage	1	1	2	2
Intraabdominal abscess	1	-	1	1
Wound infection	2	3	5	4

Table IX: Complications occurring in the early postoperative period after 140 different major reoperations in patients with Crohn's disease.

nal obstruction, biliary or urinary stones, abdominal hernia, duodenal ulcer and major complications such as intraabdominal hemorrhage, fistulae and abscesses.

Two patients died, one of them after an *anastomotic leakage* and the other one due to "hepato-renal syndrom". Two patients developed an *obstruction of the intestine*. Another two patients were re-operated upon due to *postoperative hemorrhage*, one of them three times.

The patient with a fistula between the bowel and the abdominal wall developed an *abscess in the abdomen* and drainage of that abscess had to be carried out three times before the patient recovered.

Wound infection was recorded in five patients.

PATIENTS WITH ENTERO-STOMAS

At the end of the follow-up period 41 patients had got an ileostomy and one patient a colostomy. Most of them (35 patients) endured the entero-stomas well. Three patients had problems with increased loss of intestinal fluid and another four patients had problems with their ileostomies, such as leakage and difficulties in bandaging.

QUALITY OF LIFE

Ninetynine of the surviving 125 patients (79%) were doing well at the latest clinical examination and they were able to do full time work (QL I). Seventeen patients (14%) were doing fair (QL II), while six patients (5%) were in a poor condition (QL III). The remaining three patients were at that time recently reoperated upon, and were thus not included.

DISCUSSION

The present material includes all those citizens in Malmö, Sweden, who before surgical treatment were diagnosed as having Crohn's disease during the period of investigation, 1958 - 1974. The material is unselected and the follow-up complete. During the first years of the study, patients with this disease were rather uncommon, but during the following years the incidence rose (1) and the experience in treating these patients increased. The experience that serious complications appeared during conservative treatment resulted in a shift to a more aggressive surgical approach. This shift was somewhat gradual but during the last part of the period on study, patients were operated upon earlier after onset of the disease.

The present series includes only those cases, in whom the diagnosis of Crohn's disease was established preoperatively. This was in order to enable an evaluation of the results of intentionally early surgery. The excluded patients are discussed in forthcoming reports (I, III, IV).

The treatment of patients with Crohn's disease varies between different medical centers. Some authors (10 - 14) claim that non-surgical therapy, continued as long as possible, is to be preferred and that surgery should be performed only if conservative treatment fails. The reasons for this attitude are that the recurrence rate after surgery is high and that the patients may get serious metabolic disturbances or a short bowel syndrome. Others (15 - 19) advocate a more active surgical treatment. Regardless of which policy is adhered to, many authors report that the majority of patients sooner or later need to be operated upon. Goligher (20) thus reports that 90% were operated upon, Truelove (21) reports that 93%, Bergman (22) that 95% and Cooke (23) that 96% were operated upon.

The hypothesis behind the policy for surgical treatment of the majority of the patient in the present serie was that it would be better to operate earlier in an attempt to avoid complications developing during the course of the disease and to relieve the patients' symptom earlier through surgery.

The median time between *onset and diagnosis* was short (5 months) and equal for both of the two subgroups, those with predominantly small bowel disease and those with predominantly large bowel disease, respectively, while the median time between *diagnosis and operation* was twice as long for patients with mainly colonic involvement. One explanation for this finding might be that the consequences of surgery in these latter patients are of greater magnitude, especially in younger patients. It is a great trauma to have an ileostomy for the rest of one's life,

therefore the patients and the surgeon certainly hesitate before such a procedure is performed. Nevertheless, the median time between diagnosis and operation for these patients was only eight months. In the literature, the time between onset and operation is seldom reported and thus no comparison can be done with other reports. However, when regarding the reluctant attitude to surgery that is prevailing in many medical centers, it seems obvious that the patients in the present study were operated upon comparatively early.

In the present series the frequency of intraabdominal fistulae and abscesses was low, and lower than in most published reports (10, 11, 21, 23 - 31). It is natural that a chronic disease may cause complications as time goes on, and this fact applies especially to Crohn's disease. Even if the disease activity can be low for periods it often leads to increasing inflammatory reactions and fibrous thickening of the intestinal wall, which in many cases eventually results in obstruction, intraabdominal fistulae and abscesses. The low frequency of these complications in the present study is interpreted as a result of and evidence for that patients have come early to surgery. Some complications, reported by others, such as obstructive uropathy (32, 33) and fistulae between the bowel and the bladder (34), were not seen in this series.

Among the preoperative complications occurring, anal fistulae showed the highest frequency in the present study. This is a common complication to Crohn's disease and some times (6 patients in this study), the initial manifestation of the disease. The frequency of anal fistulae depends on the site of involvement of the disease in the bowel (35, 36). Patients with Crohn's colitis are more prone to develop anal fistulae than patients with predominantly small bowel disease, and Lockhart-Mummery in 1972 (37) reported that such a fistula occurred in almost every patient with rectal involvement. In 40% of the

present cases with anal fistulae, this complication occurred after more than two years' disease history. Although some of them healed spontaneously either preoperatively or after the major operation, most of them (24 patients) required excisional therapy. It is possible that such a procedure might have been avoided if an earlier resection of diseased bowel had been performed.

It is a generally held opinion that bleeding from the bowel is less frequent in Crohn's disease than in ulcerative colitis. The frequencies reported in the literature range between 3% and 46% (10, 21, 25, 27 - 29 , 38). Even if the degree of intestinal bleeding was not defined in those studies, the frequency of hemorrhage, necessitating transfusion (11%), in the present study was in agreement with most of those figures. In eight of the 14 patients, however, the hemorrhage occurred after a disease history of at least two years, and might have been avoided with earlier surgery.

Systemic complications, such as erythema nodosum, arthritis and episcleritis/iritis often occur when the disease activity in the bowel is high (10, 39), therefore they are often seen at the onset of the disease, as in this series. The frequency of these complications in the present series were in accordance with those, reported on in many other studies (10, 21, 23, 24, 27, 29, 30, 34).

Biliary and urinary stones and gastroduodenal ulcers have not been especially searched for and no conclusion concerning the true frequency of stone formation pre- and postoperatively could be drawn from this series. However, the frequency of stones which were found accidentally or due to symptoms was in accordance with those reported on by others (23, 28, 34, 40, 41). The frequency of biliary stones in the present series (8%) was much lower than that reported by Baker et al (42).

They also found that the frequency of biliary stone formation was highly related to the duration of the disease in such way that patients with a long duration showed a higher frequency.

Most of the patients in this study were operated upon due to weight loss, pain and diarrhoea, while intraabdominal abscesses and intestinal obstruction indicated surgery in only two per cent and one per cent, respectively, figures which differ widely from other reports (12, 13, 16, 28, 43 - 45). Eleven per cent of the patients were operated upon though they had only minor symptoms of the disease, a finding that emphasizes the more aggressive surgical approach, that was prevailing in the latter part of the study.

Fulminant colitis with toxic dilatation of the large bowel is a well-recognized entity of Crohn's disease as well as of ulcerative colitis (13, 29, 45 - 48). These patients often have a rather short disease history and the deterioration of the clinical course is often rapid, as for the patients in this study.

The majority of the patients in the present study was operated upon early without preoperative septic complications. Fasth et al in 1980 (18) found that the occurrence of preoperative septic complications was the main factor correlated to the early postoperative complication rate. Similar findings are reported by Higgins et al (31) and Allsop & Lee (49). In the present study with surgery in most cases performed early, before the development of intraabdominal fistulae and abscesses, the frequency of early postoperative complications was low. This finding strongly supports the statement of Fasth et al (18), that elective surgery should be carried out before complications have developed. Another finding, emphasizing the argument for early surgery is, that the two patients, who died during the early postoperative months, both have septic complications at

the time of operation.

The frequency of late postoperative complications did not diminish with early surgery. The finding that 15% of the 131 patients, surviving the primary operation, had to be operated upon due to intestinal obstruction was in accordance with other reports (45, 50). Stitch abscesses, usually an annoying complication of minor importance, were also seen in 15% of the patients. After the introduction of absorbable suture material this complication is rarely seen. Most of the anal fistulae, developing after the primary operation, were seen in patients with recurrent disease. In 29 per cent of the patients with ileostomy, retraction of the stoma occurred and some times necessitated laparotomy for correction. The frequency of delayed perineal healing after proctectomy was the same as reported by others (16, 51, 52). The use of non-absorbable sutures may be one of the explanations for this complication, even if there is apparently a general tendency for these wounds to heal slowly.

The recurrence rate in this study was comparable with many previous studies, for example Hellers (53) and Hellberg et al (54), and also in accordance with that of the total present material including also patients with preoperatively unknown disease. When relating the risk of having a second resection to the site of the primary disease there was a statistically significant difference in favour of those with predominantly small bowel disease, a finding which was in agreement with the study by Hellberg et al (54). Some factors influencing the recurrence rates after surgery are discussed in a forthcoming report from this department (I).

The late mortality rate in this series with death associated with Crohn's disease, was low. Four patients with Crohn-lesions in the bowel (2,3%) died of intercurrent disease, two of them in the early postoperative period after reoperation. The rate

reported in the literature differs between 3% and 10% (16, 21, 50, 55, 56).

Within the past ten years there has been a growing awareness that malignancy of the bowel is a potential complication of Crohn's disease (21, 24, 45, 57, 58), especially in by-pass or excluded segments of the bowel (59). In the present study no malignancy of the intestine has been seen. This might be due to the facts that the diseased bowel generally has been resected early and that no by-pass procedures have been performed. It must be remembered, however, that the material in this respect is comparatively small and that the observation time is probably too short.

The data presented in this study seem to warrant the conclusion that the rate and severity of complications, developing pre-operatively, can be diminished if the patients are operated upon early. Since almost all patients, suffering from this chronic disease, must be operated upon sooner or later, it seems reasonable to consider an early operation in order to prevent the development of such complications and to reduce the period of illness.

The number and severity of complications occurring in the early postoperative interval also seems to be decreased, if resection is performed early. However, in patients with Crohn's colitis it is more difficult to decide when to intervene with surgery, which often ends up with an ileostomy, but certainly the patients need to be operated upon before dangerous complications emerge.

Although the recurrence rate was not influenced by early surgery, and several re-resections had to be done, most patients were in a good general clinical state of health and able to do full time work at the latest clinical examination. The risk of making a patient a metabolic cripple does not seem to be great, even if

this serious condition must not be neglected.

Surgery has an important place in the symptomatic treatment of Crohn's disease. The data presented thus suggest that surgical resection performed early may reduce the number of serious complications of the disease and the period of illness.

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III

CROHN'S DISEASE IN A DEFINED POPULATION
COURSE AND RESULTS OF SURGICAL TREATMENT
Part I: SMALL BOWEL DISEASE

by

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ABSTRACT

In a total, unselected series of all 207 patients with Crohn's disease diagnosed in 1958 - 1974, only 87 of 182 patients, operated upon during the period of investigation were at a comprehensive reevaluation found to have the disease predominantly or exclusively confined to the small bowel. In five cases the entire small bowel was more or less involved. The frequency of preoperative complications was low. The most common of these were anal fistulae, while arthritis or iritis/uveitis were not seen in any case. Fistulae after appendectomy were seen in three cases. "Kissing" lesion, i.e. diseased ileum adherent to the sigmoid, was seen in seven cases. No more serious fistulae were seen. The postoperative complications were also comparatively few including one postoperative death. The calculated recurrence rate at 15 years was 43%. A second "radical" resection for recurrence was performed in 22% with an increased risk of further recurrences. However, in spite of the fact that some patients needed repeated resections the outcome of surgery as assessed at the end of the observation time was good in most cases.

INTRODUCTION

In the original report in 1932 Crohn, Ginzburg & Oppenheimer stated, that the disease described by them would stop on the ileal side of Bauhin's valve. During the 50 years since that report was published it has, however, become obvious that Crohn's disease may appear in any part of the alimentary tract, but still the most common localization is in the distal part of the bowel, with or without involvement of the colon.

For diagnosis, radiography is the single most effective method, but in spite of improved radiological technique the diagnosis and extent of the disease is still difficult to assess in many cases. Sometimes the disease presents itself as an emergency and patients are operated upon for example as presumed appendicitis. Opinions differ whether resection should be performed in such cases or if the bowel should be left for radiological examination, and if the appendix should also be removed or not (van Patter, Bargaen, Dockerty, Feldman, Mayo & Waugh, 1954; Gump & Lepore, 1960; Schofield, 1965; Kovalcik, Simstein, Weiss & Mullen, 1977; Hellers, Ewert & Bergstrand, 1980; Fonkalsrud, Ament & Fleisher 1982).

The treatment of patients with diagnosed Crohn's disease is still under dispute since there is no causal therapy. Most patients, however, must be operated upon sooner or later due to complications (Atwell, Duthie & Goligher, 1965; Goligher, deDombal & Burton, 1972; Truelove & Pena, 1976; Bergman & Krause, 1977; Cooke, Mallas, Prior & Allan, 1980). There have also been different recommendations on whether operation should be a palliative by-pass procedure, with or without exclusion of diseased bowel, or a resection of involved intestine. During the last decade the latter type of procedure has been used more commonly.

The aim of the present investigation was to analyse the sub-localizations of the disease in a total, unselected material of Crohn's disease, and to study the diagnosis and the outcome of resectional treatment in the subgroup of patients with predominantly or exclusively small bowel disease.

PATIENTS AND METHODS

All patients diagnosed as having Crohn's disease in the defined population of Malmö, Sweden, during the years 1958 through 1973 were traced by Brahme, Lindström & Wenckert (1975) in an epidemiological survey. With the addition of the corresponding patients from the following year and after reexamination as described below, 207 patients altogether were found to have Crohn's disease diagnosed during 1958 through 1974. In twelve of these patients the disease was confined to the appendix vermiformis, and another 13 patients were diagnosed but not operated upon during the investigation period. These 25 patients were excluded from this study and are discussed in forthcoming reports (II, V).

Of the remaining 182 patients, 170 were subjected to a resection of all macroscopically involved intestinal tissue ("radical" resection), with the exception of the rectum in some cases. In twelve patients only part of the diseased bowel was resected.

The small bowel was radiographically examined by the conventional follow-through technique until 1972, from which year the enteroclysis technique described by Sellink (1971) was increasingly used instead. The large bowel was examined by the double contrast method described by Welin (1962).

The policy was to open the specimens during the operation and examine them in order to avoid resection in grossly diseased

bowel, if possible. As a rule, specimens after preparation were measured and macrophotographed in all cases, except for those operated upon during the first few years of the investigation period. The opened bowel specimens were then fixed in 10% formalin solution on large specially made trays to preserve good morphology. After fixation a large number of histological sections from the bowel and the lymph nodes were prepared and examined.

All patients were postoperatively checked up at Malmö General Hospital. The policy was to perform radiological examinations within the first postoperative year and to examine the patients clinically more often during the first year. Thereafter most of the patients were examined clinically yearly. Twentysix patients later on moved out from the city and were thereafter checked up elsewhere. The results of these examinations were included in this analysis.

At the end of the follow-up period, December 31st, 1979, the median time between the primary operative procedure and the latest clinical examination or the date of death was 9.2 years (mean 10 years, range 9 months - 19.6 years).

All records, radiograms, histopathological sections from biopsies and specimens have been kept (since 1969, the whole specimens). Thus, it was possible to perform a thorough reexamination of all available material and data, including case histories, operative findings etc. This evaluation was performed by the authors, i.e. four surgeons, one radiologist (JH) and one pathologist (CL).

The diagnosis was in all cases based on histopathological examinations of surgical specimens using the criteria reported by Lockhart-Mummery & Morson (1964) and Price & Morson (1977). Non-caseating giant cell granulomas were found in the resected bowel in 83% of the cases and in removed lymph nodes in 60%.

The radiographic criteria used were in accordance with those reported by Sellink (1971), Laufer (1977) and Hildell (1979).

The definition of recurrent disease was in accordance with the "Cape Town classification" in which recurrence is defined as the appearance of objective signs - radiologically, endoscopically or histopathologically - of Crohn's disease in the bowel of a patient who previously had a resection of all macroscopically diseased tissue (Lee & Papaioannou, 1980). Recurrence rates were calculated both with crude figures and according to the actuarial method (Hill, 1966; Andersen & Bonnevie, 1971).

As assessed at the reevaluation the patients were finally divided into three groups, according to the degree of general health - "quality of life" - at the latest clinical examination, which in all surviving patients was performed during the second half of 1978 or during 1979. The definitions of the groups were:

Quality of life I: The patient was in a good general state of health, able to do full time work and to have normal leisure time activities.

Quality of life II: The patient was able to work part time and the leisure time activities were restricted due to diarrhoea, pain etc.

Quality of life III: The patient could not work at all and all the leisure time activities were severely restricted due to, for example, frequent diarrhoea, general weakness or pain.

RESULTS

I. Number of patients with small bowel disease in the total material.

Age and sex distribution.

At the reevaluation it was found that the frequency of patients with Crohn's disease exclusively or predominantly confined to the small bowel was 48% of those operated upon (87/182 patients).

There were 39 males and 48 females. The age of the patients at the time of the primary operative procedure ranged from 10 to 79 years with most, 49, of them between 16 and 30 years of age (median 26 years, mean 30 years) (fig 1).

II. Preoperative diagnosis and extent of the lesions.

In 21 cases the primary operation was performed as an emergency one without preoperative radiological examination. The remaining 66 patients underwent altogether 115 small bowel and 109 large bowel examinations. The diagnosis of Crohn's disease was preoperatively radiologically established in 60 of these 66 patients (91%). In the remaining six patients the preoperative diagnosis were the following: Appendiceal abscess (2 patients), malignancy (3) and irradiation injury (1).

In twelve of the 60 cases the disease was discovered at a previous appendicectomy, performed as an emergency in eleven cases and as an elective operation in one patient. The involved ileum was in all cases left at this operation and the patients were radiographically examined, in order to assess the extent of the disease as thoroughly as possible. In eight of these twelve patients the major procedure was then performed within a few months but in the remaining four cases the time between appendicectomy and primary major operation ranged between one and six years. The reason for this delay was that the patients

No of patients

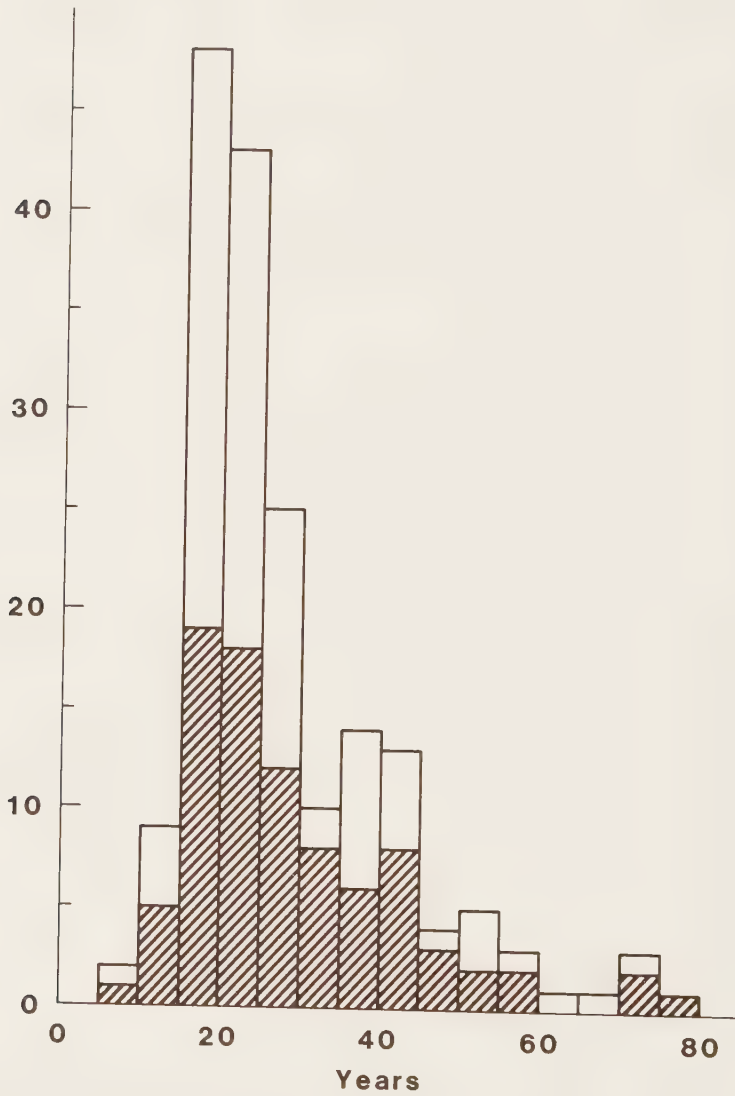


Figure 1: Age at the time of the primary operation in patients with Crohn's disease.
 Hatched area= patients with predominantly or exclusively small bowel disease.

initially had no subjective symptoms.

The median duration time between diagnosis and operation for the 60 patients with preoperatively established diagnosis was four months (mean 12 months, range 1 month - 7.7 years).

The extent of the lesions in the bowel, as assessed at the reevaluation, was the following: Fifty patients had lesions both in the terminal ileum and in the cecum (including three cases with the disease confined to the cecum). In 28 cases the lesions were confined to the terminal ileum, while four patients had lesions macroscopically limited to the ileum, proximal to its distal part. In five patients the entire small bowel was more or less involved.

The extent of the disease in the distal ileum and the cecum, as seen on radiograms, was in accordance with that found at the time of operation in all cases but one. The extent of the disease, however, in the small bowel proximal to the distal part of the ileum could not be assessed radiographically, since the radiographic methods used for examinations of the small bowel had a low diagnostic accuracy in the detection of minor "skip lesion" proximal to the mainly involved segment.

III. Preoperative complications

During the preoperative interval various systemic and local complications developed.

Systemic complications

Erythema nodosum was seen in two patients, while duodenal ulcer was recorded in four patients. Retardation of growth and stunting of sexual development were seen in three patients, and amenorrhea in another five patients.

Arthritis, urinary stones or complications involving the eyes, such as episcleritis or iritis, were not seen in any

patient during the preoperative interval.

Local complications

Anal fistulae were recorded in six patients. An entero-cutaneous fistula between the cecum and the abdominal wall developed in two cases after appendicectomy, while another patient had an abscess in the abdominal wall after this procedure. In another three patients an abscess in the abdominal wall occurred. Intestinal hemorrhage, necessitating blood transfusion, occurred in two patients.

"Kissing" lesions: An encroachment of the otherwise uninvolved sigmoid colon from the adjacent diseased distal ileum was pre-operatively seen on radiograms in nine patients. In two of these nine cases, however, this finding was not confirmed at the time of the operation. At laparotomy the large bowel could be separated from the diseased ileum without colonic resection.

IV. Preoperative treatment

Treatment with corticosteroids was tried in ten patients, in one patient combined with sulphasalazine (Salazopyrine^R) and in another one with azathioprine (Imurel^R). Twelve patients were treated with sulphasalazine only. The period of treatment ranged from one to nine months.

V. Indications for surgery

As seen in table I, 39 patients were operated upon due to persisting or progressing symptoms. Nine patients, with objective signs of the disease, as shown by radiography, endoscopy and/or blood chemistry, were operated upon though they had only minor symptoms. In another nine cases suspicion of appendicitis was the indication for surgery, while in two cases a presumed appendiceal abscess indicated laparotomy. Eight patients were subjected to an emergency operation due to intestinal obstruction.

Entero-cutaneous fistulae/abscesses, complicating previously performed appendicectomy or drainage of abscesses, were the indications in six patients, while anal fistulae, suspicion of malignancy and stunting of growth indicated surgery in nine patients.

Main indication	Number of patients
Weight loss, pain, diarrhoea	39
Minor symptoms	9
Appendicitis	9
Intestinal obstruction	8
Entero-cutaneous fistulae/abscesses	6
Suspicion of malignancy	3
Appendiceal abscess	2
Anal fistula	4
Stunted growth/sexual development	2
Miscellaneous	5
87	

Table I: Main indications for surgery in patients with Crohn's disease predominantly or exclusively confined to the small bowel.

VI. Primary operation

The primary operative procedures are listed in table II. The most common operation was ileocolic resection (ileocecal resection/right hemicolectomy). In 82 patients "radical" resections were performed. The remaining five patients were palliatively operated upon.

Operative procedures	"Radical" resection	Palliative resection	Total number of patients
Small bowel resection	5	4	9
Ileocolic resection	77	1	78
Total number of operations	82	5	87

Table II: Primary operative procedures in patients with Crohn's disease predominantly or exclusively confined to the small bowel.

VII. Early postoperative complications

During the first operative month after the primary operation the following complications occurred: One patient died due to sequelae of an *anastomotic dehiscence*. Three patients were operated upon due to *intestinal obstruction*. Wound infections occurred in seven patients. Two patients developed an *intraabdominal abscess*, and another patient an *entero-cutaneous fistulae* while in yet another patient a *recto-vaginal fistulae* occurred.

Minor septic complications, such as pneumonia or fever (more than 38°C) of unknown origin occurred in twelve patients.

VIII. Late complications

During the follow-up time ten patients were operated upon due to *intestinal obstruction*. Biliary stones were seen in five patients and urinary stones in 13, five of whom were operated upon for that reason.

There was radiographic evidence of *duodenal ulcer* in two patients. *Stitch abscesses* (non-resorbable suture) occurred in nine patients. One patient developed *Bechterew's disease* and another patient was reoperated upon due to an *abdominal hernia*, developing after re-operation.

IX. Recurrence and "quality of life" at the latest clinical examination

During the observation time 47 of the surviving 81 patients (58%), subjected to a "radical" resection were free from recurrence of the disease (fig 2 and table III). Most of these patients (43) were doing well (QL I). Another three patients had no intestinal symptoms but were doing fair (QL II) due to intercurrent diseases. The remaining patient died due to intercurrent disease, without lesions in the bowel as seen at the autopsy.

Recurrence developed in 34 patients (42%). The cumulative recurrence rate, calculated according to the actuarial method, was at 15 years 43%. The site of recurrent lesions was in 31 cases in the oral part of the anastomosis, and on both sides of the anastomosis in three other cases, primarily subjected to an ileocecal resection. Postoperative radiological examination of the small bowel was performed in all cases with the exception of one patient, who was reoperated upon early due to clinical symptoms.

A second "radical" resection due to recurrence was carried out in 18 cases (18/81 patients = 22%). Another two patients underwent laparotomy due to recurrence, in one of them a by-pass procedure was performed and in the other patient explorative laparotomy only. The first patient died in the early postoperative month, while the second patient had extensively scattered lesions in the small bowel at the time of the laparotomy. In spite of this he was doing well at the latest clinical check-up.

Ten of the 14 patients with recurrence, not reoperated upon, showed clear radiographic evidence of recurrent disease as seen on repeated examinations, but none of them had clinical symptoms ("radiological recurrence"). Another patient had only minor problems with diarrhoea (QL I). One patient was doing fair (QL II) and was on treatment with azathioprine (Imurel^R), while another patient suffered from anal incontinence after excision of an anal fistula (QL III). One patient died of intercurrent disease.

In four of the 18 patients subjected to a second resection, there was no evidence of recurrent disease postoperatively. Three of these four patients were doing well (QL I) while the fourth patient was doing fair (QL II). One patient was at the latest clinical examination recently reoperated upon and the quality of life was not evaluated. Another 13 patients, however, developed recurrence again and four of them underwent a third resection, while one patient was found to have widespread lesions in the bowel at an explorative laparotomy. Of the remaining eight patients four were doing well (QL I) while another three were doing less fair (QL II) due to diarrhoea and pain. The remaining patient was in a poor condition as a result of recurrent disease (QL III).

Three of the four patients who underwent a *third resection* developed recurrence again. Two of them, however, were in a good general state of health at the latest clinical examination, while another patient had to undergo further resections. The fourth patient was at that time recently reoperated upon with an observation period of less than six months after that operation, and quality of life was not evaluated.

Five patients were *palliatively operated upon* (table III). One of them died of intercurrent disease, six years after the primary operation. Three of the remaining four patients were

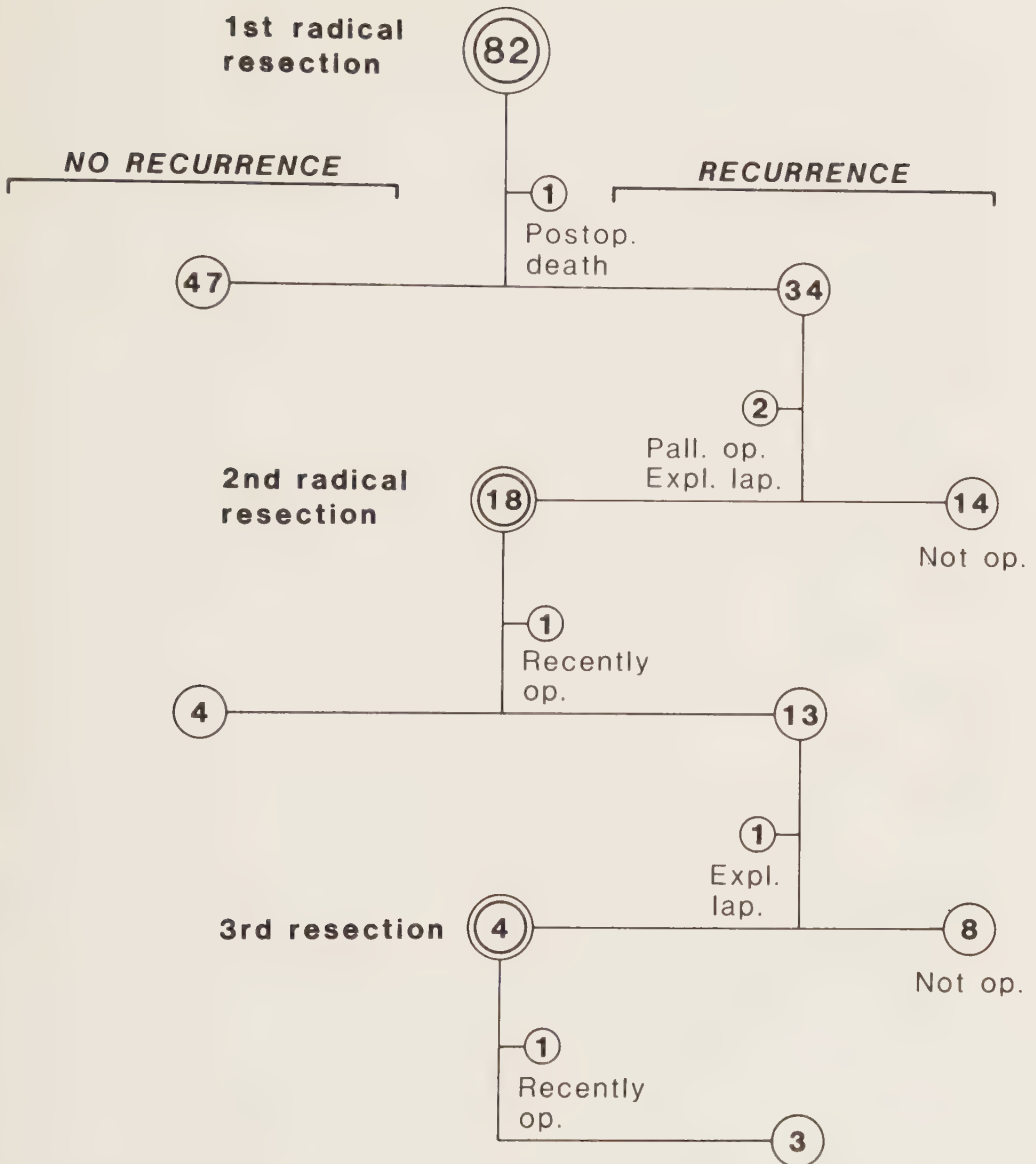


Figure 2: Outcome of primary "radical" resection in patients with Crohn's disease predominantly or exclusively confined to the small bowel.

	"Quality of life"			Deaths	Recently reoperated upon	Total number of patients
	I	II	III			
Early postoperative death				1		1
Patients without recurrence after first resection	43	3		1		47
Patients with recurrence						
Not reoperated upon	11	1	1	1		14
Pall. bypass or explor lap after first resection	1			1		2
After second resection no recurrence	3	1			1	5
After second resection, recurrence not operated upon	4	3	1			8
Explor lap after second resection	1					1
After third resection	2	1			1	4
Palliatively operated upon	3	1		1		5
	68	10	2	5	2	87

Table III: Outcome of surgery at the latest clinical examination after different operations in patients with Crohn's disease predominantly or exclusively confined to the small bowel.

doing well (QL I), one of them was treated with sulphasalazine (Salazopyrine^R). The fourth patient had problems with diarrhoea and subacute partial obstruction (QL II) but refused further operations.

X. Total length of resected small bowel in relation to quality of life

Seventy-three of the 77 patients, primarily operated upon with a "radical" ileocolic resection or right hemicolectomy, were alive at the latest clinical examination. In 70 of these 73 patients data concerning the total length of the resected ileum after all operations were available. In nine of these 70 patients, resection less than 30 cm was performed. In another 27 patients between 30 and 60 cm were excised, while in the remaining 34 patients more than 60 cm of the small bowel was resected (table IV).

	< 30	30 - 59	> 60 cm
QL I	9	26	23
II	-	1	6
III	-	-	2
Recently reop upon			3
	9	27	34

Table IV: Total length of resected small bowel in relation to "quality of life" (QL) at the latest clinical examination in patients with Crohn's disease predominantly confined to the small bowel and primarily operated upon with ileocecal resection/right hemicolectomy.

When relating the total length of the resected ileum to "quality of life" at the latest check-up, it was found that all patients but one, in whom less than 60 cm had been excised, were doing well (QL I). The remaining patient suffered from diarrhoea (QL II). In the group of patients in whom more than 60 cm of the small bowel was resected, 23 were doing well (QL I). Five of six patients, who were doing less fair (QL II)

had diarrhoea, and the sixth patient suffered from pain. Two patients, on treatment for recurrence, were in a poor condition (QL III) due to diarrhoea and pain. Three patients were at the latest clinical examination recently reoperated upon and it was not possible to evaluate "quality of life".

XI. Late mortality

During the late postoperative observation time four patients died (table III). One patient died due to pulmonary embolism soon after a second by-pass procedure for recurrence. The remaining three patients died of intercurrent disease, 3, 6 and 11 years, respectively, after the initial operation. Two of them had Crohn-lesions in the bowel seen at the autopsy. Thus, the late mortality rate was 3.5%.

DISCUSSION

The patients reported on in this study were residents in a defined population, consecutively operated upon for Crohn's disease. The patients were not selected in any way. The data concerning diagnosis, treatment and follow-up were complete. During the first part of the investigation period only a few patients suffered from Crohn's disease, but as the incidence rose (Brahme et al, 1975) the experience of treatment increased. Due to some serious complications developing in patients not operated upon during the first few years, the attitude towards surgery gradually became more aggressive, and the patients were operated upon earlier. In the present study all patients operated upon were included. The outcome of intentionally early surgery in those patients with preoperatively known Crohn's disease is analysed in a forthcoming report (II).

At the reevaluation performed it was shown that less than 50% of all cases had lesions exclusively or predominantly

in the small bowel. The most common localization of Crohn's disease in the bowel is the classical one, in the distal ileum, as described by Crohn et al (1932), and this was also the finding in the present study. Only ten percent of the patients had lesions proximal to the distal part of the ileum. Isolated involvement of the stomach or the duodenum was not seen in this series.

The high frequency of correctly diagnosed cases in patients with small bowel disease is probably explained by the fact that the macroscopical lesions in the distal ileum are often pronounced before clinical symptoms occur and the patient thereby comes to radiography. This is to compare with patients with wide-spread lesions in the small bowel, or with involvement of the large intestine, in whom the clinical symptoms seem to occur earlier. The lesions in the distal ileum in these patients may be more difficult to assess radiographically.

The presence of non-caseating giant cell granuloma is the most distinctive diagnostic feature of Crohn's disease, and such granulomas were found histopathologically in the resected specimens in more than 80% of the patients in this study. The reason for this high rate is certainly the fact that a large number of histological sections of the tissues have been examined. The frequencies of granuloma in other series vary between 23% and 75% (Warren & Sommers, 1948; Lockhart-Mummery & Morson, 1964; Hardin & Friesen, 1973; Assarsson & Räf, (1974). However, Lockhart-Mummery & Morson in 1964 found granulomas in 87% of resected large bowel specimens.

Since the most common involvement of the bowel is the distal ileum it is not surprising that some patients are operated upon with the presumptive preoperative diagnosis of appendicitis or appendiceal abscess, as were 23 patients in this

study. Acute resection of diseased bowel was performed in eleven of these cases, due to the severity of the lesions. In the remaining 12 patients the diagnosis was established at laparotomy but the lesions were not so pronounced and appendicectomy as the only procedure was carried out, leaving the remaining part of the bowel for further radiological examination of the extent of the lesions.

It has been pointed out, that there is a risk of developing an entero-cutaneous fistula, if only appendicectomy is performed in patients with Crohn's disease (Crohn et al; Gump & Lepore; Schofield; Kovalcik et al; Hellers et al; Fonkalsrud et al). Some authors state, that appendicectomy is safe if the cecum is uninvolved (van Patter et al; Gump & Lepore; Marx; Kewenter, Hultén & Kock, 1971; Korelitz & Sommers, 1973), while others have found that such a procedure should be avoided (Fonkalsrud et al).

The frequency of entero-cutaneous fistulae after appendicectomy in the present study (25%) was in agreement with those reported by others (van Patter et al; Colcock & Vansant, 1960; Hellers et al).

The fact that such fistulae may develop after appendicectomy in this situation may indicate that this procedure should not be carried out. However, inflammatory lesions in the distal ileum are not always due to Crohn's disease. Infection by *Yersinia enterocolitica* (Sjöström, 1971; Marks, Pay, Lafleur, Lackmann & Hammerberg, 1980) or *Yersinia pseudotuberculosis* (El-Maraghi & Mair, 1979) can have similar macroscopical features in this part of the bowel as Crohn's disease. Since these diseases heal spontaneously it might be dangerous to leave the uninvolved appendix in a patient with an abdominal scar, indicating that appendicectomy has been performed. But on the other hand, one must be well aware of the risk that a fistula may develop if the patients have Crohn's disease.

Therefore, no general recommendation can be given whether appendicectomy should be performed or not.

Fistulae between the inflamed distal ileum and the otherwise uninvolved sigmoid colon are sometimes seen but not in the present series. They probably occur in cases where the diseased ileum adheres to the colon - "kissing" lesions - before a fistula develops. In the present series where such lesions occurred, the loops were merely separated without colonic resection. Since no complications occurred, this policy is recommended unless a fistula has already developed.

The recurrence rate in this study was comparable with that in other reports (deDombal, Burton & Goligher, 1971 a; HELLERS, 1979; Selby, Kater, Heap & Gallagher, 1979; Hellberg, Hultén, Rosengren & Åhrén, 1980; Higgins & Allan, 1980; Lock, Farmer, Fazio, Jagelman, Lavery & Weakley, (1981).

The site of recurrence in the bowel was always adjacent to the anastomosis, and in all cases but three on the proximal side. The same finding has also been reported by Fasth, Hellberg, Hultén & Åhrén, 1981) and they strongly recommended that, whenever possible, colonic resection should be limited in surgery for patients with the disease localized to the classical region.

In the present study the recurrence rate after a second resection was higher than the recurrence rate after the initial operation. Similar findings have been demonstrated by others (van Patter et al; Lennard-Jones & Stalder; HELLERS). The recurrence rate, however, after a second "radical" resection in patients with exclusively or predominantly colonic disease in this series was much lower, 36%, as assessed in a forthcoming report (I).

The histopathological appearances are, in a forthcoming report (I), shown to have prognostic implications on the recurrence rate. Patients with macroscopically uninvolved resection lines but with microscopical lesions, such as ulcers, crypt abscesses and giant cell granulomas in the margins were more prone to develop recurrence than patients without such lesions.

The mortality rate in this study was low, with early postoperative death seen in 1.2%. Such a low rate has also been reported by Colcock & Vansant; Homan & Dineen (1978), Hellers, Kåresen, Serch-Hanssen, Thoresen & Hertzberg (1981) and Hellberg et al, while others have reported a high rate (van Patter et al; deDombal, Burton & Goligher, 1971 b).

Late death associated to Crohn's disease was seen in 3.5% in this study and this rate was similar to, for example, that found by Lennard-Jones & Stalder, but lower than others reported (Davis & Chir, 1961; Stone, Veidenheimer, Corman & Collier, 1979; Higgins & Allan).

As stated by others (Allsop & Lee, 1978; Higgins, Allan, Keighley, Arabi & Alexander-Williams, 1980; Fasth, Hellberg, Hultén & Magnusson, 1980) there is a strong correlation between the occurrence of septic complications (intraabdominal fistulae, abscesses etc) at the time of surgery and the development of early postoperative complications. The low frequency of early postoperative complications and the low postoperative mortality rate in the present study may be due to the fact, that many patients were operated upon comparatively early, before serious septic complications occurred, and that the policy was to perform "radical" resections.

A common objection to surgery is that resections, especially extensive and repeated, may result in serious metabolic disturbances or a short bowel syndrome. Surgery, according to some authors, should therefore only be carried out as an ultimate

treatment (Marshak, Lindner & Janowitz, 1966; Alexander-Williams, 1971; Stock, Müller & Nohr, 1979). The outcome of surgery in this study does not support such a conservative attitude. Even if there were patients with some or considerable disability at the latest clinical examination, most of them (83%) were doing well.

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IV

CROHN'S DISEASE IN A DEFINED POPULATION
COURSE AND RESULTS OF SURGICAL TREATMENT
PART II: LARGE BOWEL DISEASE

by

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ABSTRACT

In a total, consecutive series of 182 patients operated upon for Crohn's disease 52% had the lesions predominantly or exclusively confined to the colon. It was found that skip lesions were only apparent. Either was the entire colon involved or were the lesions confined to the right hemicolon. The most frequent preoperative complications were anal fistulæ erythema nodosum and arthritis, the latter, however, only seen when the disease was in an active stage. A "radical" operation was performed in 88 of the 95 patients. The general policy was to spare the rectum, if possible. It was found that when the rectum was primarily involved the lesions did not disappear after subtotal colectomy. Ileorectal anastomosis, performed in 22 cases, was only successful in nine. In all these nine cases the rectum was uninvolved preoperatively. The overall mortality rate related to Crohn's disease was 6%. The overall recurrence rate was high (62%). All patients with an anastomosis between a disease-free small intestine and a diseased colon developed recurrence in the ileum. Therefore, a thorough preoperative examination of the colon is essential. In spite of repeated reoperations 76% of the patients were doing well at the latest clinical examination.

INTRODUCTION

During the last two decades Crohn's disease of the colon has been well recognized and reported to occur in rising frequency. Earlier many such cases were probably erroneously diagnosed as ulcerative colitis.

Treatment is usually started conservatively and the indications for surgery in cases with total colitis are often less liberal than in cases with terminal ileal disease, since resection often necessitates the performance of an ileostomy.

Surgery in patients with Crohn's colitis may imply various procedures, for example right hemicolectomy, segmental resection, subtotal colectomy or proctocolectomy. Opinions differ whether the rectum should be spared or not.

The aim of the present study was to determine, in an unselected series of consecutively operated patients, the number of patients with colonic involvement, and in more detail analyse the course and treatment of the disease. Special interest was paid to different surgical procedures and to the fate of the rectum.

PATIENTS AND METHODS

For details concerning patient material, preoperative radiographical examinations, management of the specimens, radiographic and histopathological criteria used, postoperative examinations, definition of recurrence and statistical methods reference is made to part I of this report (III).

For completeness and comparative purposes this report also includes a presentation of all patients with "indeterminate colitis", operated upon during the same investigation period.

RESULTS

I. Number of patients with large bowel disease in the total material.

Age and sex distribution.

At the reevaluation it was found that the frequency of patients operated upon for Crohn's disease exclusively or predominantly confined to the large bowel was 52% (95/182 patients).

There were 40 males and 55 females. The age of the patients at the time of the primary operative procedure ranged from 10 to 75 years, and most (67) of them were between 16 and 30 years of age (median 22 years, mean 27 years).

II. Preoperative diagnosis and extent of the lesions

Preoperative radiological examinations were performed in 92 of the 95 patients (150 small bowel and 257 large bowel examinations). The remaining three patients were urgently operated upon without radiological examination.

The diagnosis could radiologically be assessed in 69 of the 92 patients (75%). In two cases there was no firm diagnosis but in one of those the clinical diagnosis was Crohn's disease. In the remaining 21 patients the radiographic diagnosis was not correct. The most frequent erroneous diagnosis was "ulcerative colitis" (18 patients).

Even if the radiological diagnosis, however, was ulcerative colitis, the surgeons judged three of these 18 patients to

have Crohn's disease before the abdomen was opened. The reasons for this judgement were the presence of giant cell granulomas in a biopsy from the rectum (1 patient), the absence of left colon involvement (1) and the absence of rectal lesions (1). Two of the remaining three patients with incorrect diagnosis were supposed to have a malignancy in the bowel, while the radiographical diagnosis in the third patient was "polyposis coli". Thus, in 73 patients the preoperative diagnosis was correct.

The median time between *diagnosis and operation* for these 73 patients was eight months, mean time 18 months (range 1 month - 12 years). The corresponding figures for the 15 patients with a presumptive diagnosis of ulcerative colitis were: median time 3.2 years, mean time 5.5 years (range 1 month - 17 years).

The extent of Crohn's disease in the bowel in all of the 95 patients, as assessed at the reevaluation performed, is seen in fig 1. The extent of the lesions as demonstrated on preoperative radiograms was in accordance with that found at the time of the operation and at microscopy of resected specimens in 67 of the 92 radiographically examined patients, while it was uncertain in three. In the remaining 22 patients lesions in the distal ileum (2 patients), the right hemi-colon (4), the left hemicolon (9), the entire colon (6) and the rectum (1) were overlooked at radiography. In 11 of these cases resection of the diseased segments was performed but in the other 11 cases lesions in the large bowel were left behind.

One of the patients had coexisting lesions in the duodenum, as seen endoscopically.

V. Indications for surgery

The indications for the primary operation are shown in table I.

<u>Main indication</u>	<u>Number of patients</u>
Weight loss, pain, diarrhoea etc	54
Anal fistula	9
Intestinal obstruction	7
Minor symptoms	5
Stunted growth/sexual development	3
Fulminant colitis	3
Suspected appendicitis	2
Intestinal hemorrhage	2
Intraabdominal abscess	1
Entero-cutaneous fistula	1
Recto-vaginal fistula	1
Miscellaneous	7
	95

Table I: Main indications for surgery in patients with Crohn's disease predominantly or exclusively confined to the large bowel.

The majority (54) of the patients were operated upon due to weight loss, pain etc. The indications for surgery in those 15 cases, preoperatively classified as ulcerative colitis, were stricture of the bowel (6 patients), suspicion of malignancy (3), anal fistula (3), intestinal bleeding (1), recto-vaginal fistula (1) and fulminant colitis (1).

Fulminant colitis with toxic dilatation of the colon was also the reason for emergency operations in another two patients.

Five patients, with objective signs of the disease as shown by radiography, endoscopy and/or blood chemistry, were

operated upon though they had only minor symptoms. Three patients underwent surgery because of retardation of growth and/or sexual development.

Two patients were thought to be suffering from appendicitis, while another patient developed an entero-cutaneous fistula after previously performed appendicectomy. Yet another patient with a fistula between the distal ileum and the sigmoid colon as mentioned above, was operated upon due to this complication.

VI. Primary surgical procedures:

A. Patients "radically" operated upon (88 patients)

1. Ileocolic resection and anastomosis

There were 26 patients who underwent resection of various lengths of the distal ileum and the right colon with anastomosis (table II). At the reevaluation it was apparent that ten of these patients had lesions in the entire colon with the exception of the rectum, and that another five patients had involvement of the rectum as well. In these 15 cases the anastomosis was performed between a microscopically healthy small intestine and a diseased colon, even if the resection margins were uninvolved. The reasons for this were that lesions in the left colon were overlooked at radiography (11 patients) or that the surgeon judged the colon to be normal though he knew there had been lesions in the left colon, as demonstrated by radiography (4 patients). All these 15 patients developed recurrence in the ileum, while relapse of the persisting disease in the large bowel was seen in 11 patients. However, in the remaining four patients, no signs of active disease of the colon were seen postoperatively.

Disease recurrence of the 11 patients with lesions in the right colon only, as assessed at the reevaluation, occurred

in four patients, in all cases proximal to the anastomosis, which was thus performed to an apparently uninvolved colon.

Operative procedures	No of patients radically opera- ted upon	No of patients palliatively operated upon
Ileocolic resection and anastomosis	26	1
Ileocolic resection + enterostoma		3
Colectomy + IRA as a one-stage procedure	11	
Colectomy + temporary ileostomy	11	
Colectomy + permanent ileostomy	29	1
Proctocolectomy	7	
Small bowel resection		2
Miscellaneous procedures	4	
	88	7

Table II: Primary operative procedures in patients with Crohn's disease predominantly or exclusively confined to the large bowel.

IRA = ileorectal anastomosis

2. Colectomy and ileorectal anastomosis

One-stage procedure

An ileorectal anastomosis after subtotal colectomy as a one-stage operation was performed in 11 patients. In four of them the results were good, while in six cases recurrence in the ileum and the rectum developed. One patient died in the immediate postoperative period due to sequelae of an anastomotic leakage.

Five of the six patients with recurrent disease had to have the anastomosis resected and have an ileostomy, and in three of them the rectum was eventually excised.

Two-stage procedure

A subtotal colectomy with ileostomy was performed in 40 patients, sparing the rectum for an ileorectal anastomosis as a secondary procedure. In 26 of these cases the rectum was involved at the time of the primary procedure.

In 11 cases the continuity of the bowel was subsequently reestablished. In two of these 11 patients, recurrent disease in the ileum was found and resected at the second procedure. In six of the 11 cases the results were favourable, while in the remaining five disease recurrence developed on either side of the anastomosis. In four of these five patients the involved rectum had to be excised, while one patient still has a diseased rectum left with an ileorectal anastomosis.

Outcome of colectomy and ileorectal anastomosis

To summarize the outcome of colectomy and ileorectal anastomosis, carried out as one- or two-stage procedures, 22 such operations were performed (table III). In ten patients the restoring of the intestinal continuity was successful. In seven patients the rectum had to be excised, and in four patients it was left diseased. Two of these four patients had to have an ileostomy.

	One-stage procedure	Two-stage procedure
	Number of patients	
No recurrence	4	6
Postoperative death	1	-
Recurrence, rectum excised	3	4
Recurrence, rectum left diseased, ileostomy	2	-
Recurrence, rectum left diseased, in continuity	1	1
	11	11

Table III: Outcome of colectomy and ileorectal anastomosis in patients with Crohn's disease predominantly or exclusively confined to the large bowel.

Only one of the ten patients without recurrence in the ileum, had rectal involvement at the time of surgery, and this patient later on developed a recto-vaginal fistula. In the group of patients with recurrence six out of eleven patients had rectal lesions. Thus, when the rectum was primarily uninvolved, the result was favourable in 2/3 of the patients.

3. Colectomy with permanent ileostomy

This operative procedure was performed in 29 patients (table II and fig 2). In 18 of them no evidence of recurrent disease

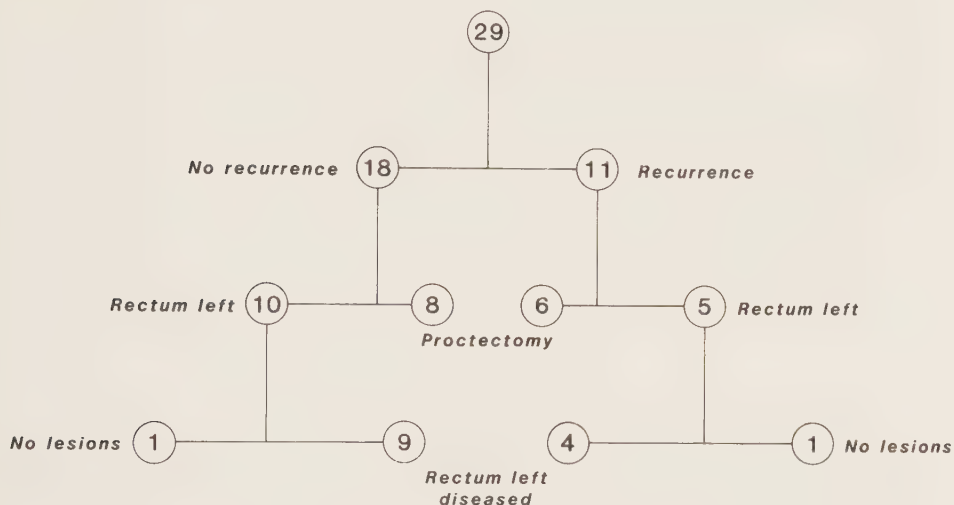


Fig 2: Outcome of primary colectomy with permanent ileostomy in patients with Crohn's disease predominantly or exclusively confined to the large bowel.

was seen during the observation time. In eight of these 18 patients the rectum was excised later on and of the remaining ten patients, nine had more or less problems with pain, discharge of purulent fluid etc from the rectum. Recurrent disease in the ileum was seen in 11 cases ($11/29 = 38\%$). Proctectomy was eventually performed in six of them, while four of the remaining five patients had problems with the diseased rectum.

4. Proctocolectomy

In seven patients a proctocolectomy was performed, in six of them the preoperative diagnosis was ulcerative colitis

(table II). In three patients no signs of recurrence were seen while the remaining four patients have been reoperated upon for that reason.

5. Miscellaneous procedures

Three patients underwent proctectomy as the only primary operation, and in another patient resection of the sigmoid colon was performed (table II). The management of these four patients was diverging from the policy due to incomplete and non-conclusive preoperative examinations. In two of them there were no signs of active disease postoperatively but the remaining two patients both had a relapse of persisting colitis.

B. Patients palliatively operated upon (7 patients)

Two patients were subjected to resection of the most heavily involved segments of the small bowel with anastomosis (table III). In another four patients ileocolic resection was performed, in two of them with a diverging ileostomy and in one patient with a colostomy at the same time. The remaining patient underwent colectomy with ileostomy.

VII. Early and late postoperative complications

Early complications

During the first postoperative month after the primary operation dehiscence of the anastomosis developed in one patient, and this patient died due to sequelae of this complication.

Ten patients were reoperated upon due to *intestinal obstruction*. *Wound infections* occurred in seven patients, while an *intra-abdominal abscess* developed in another three patients. One patient was reoperated upon due to *intraabdominal hemorrhage*.

Late complications

Nineteen patients were operated upon due to *intestinal obstruction* during the observation time, four of them more than once. Twenty-one patients had *problems with their ileostomies* (retractions, prolapses or fistulae).

Arthritis was postoperatively seen only in three patients with recurrence. None of the patients developed *iritis/episcleritis*.

VIII. Total length of resected ileum in relation to quality of life

The total length of the resected small bowel was related to the "quality of life" at the latest clinical examination. It was found that less than 30 cm were resected in ten patients, all of them were doing well (QL I).

In another 37 patients, a total length of between 30 and 60 cm had been resected. Twenty-eight of these patients were regarded as QL I, while five patients had problems with loss of intestinal fluid (2 patients), urinary stones (1), Bechterew's disease (1) or anal abscess (1) (QL II). Another patient was in a poor condition due to recurrence (QL III).

In 36 patients more than 60 cm of the small bowel were resected, in 11 of these more than 100 cm. Most of them (26) were doing well (QL I) but six patients were judged as having QL II and two patients as QL III. Four of these eight patients had extensive loss of intestinal fluid.

IX. Fate of the rectum postoperatively

At the time of the primary operation 50 patients had lesions in the rectum. During the observation time another ten patients developed inflammatory changes in the rectum. The results concerning the rectum are seen in table IV.

Primary operation	Number of patients	Rectum:			
		Left free of disease	Left diseased	Excised	Postop death
Ileocolic resection	27	17	8	2	-
Ileocolic resection + enterostoma	3	-	1	2	-
Colectomy + IRA	22	12	2	7	1
Colectomy + permanent ileostomy	30	2	14	14	-
Proctocolectomy	7	-	-	7	-
Small bowel resection	2	2	-	-	-
Miscellaneous op	4	1	-	3	-
	95	34	25	35	1

Table IV: Fate of the rectum in patients with Crohn's disease predominantly or exclusively confined to the large bowel.

IRA = ileorectal anastomosis

One can see that in 35 of these 60 patients with a diseased rectum, proctectomy was performed, while the diseased rectum was left in the remaining 25 patients.

When the rectum was primarily involved, the lesions did not disappear after primary colectomy and ileostomy.

Delayed perineal healing - more than three months - after proctectomy occurred in 16 patients ($16/35 = 46\%$). The median time for healing in these patients was 11 months (mean 1.8 years, range 3 months - 6.8 years).

X. Overall results: mortality, recurrence rate, number of patients with entero-stomas and quality of life

During the follow-up period nine patients died (table V): one patient (1%) died in the early postoperative period in sequelae of anastomotic dehiscence after colectomy and ileo-rectal anastomosis as a primary procedure. Another two patients died in the early postoperative period after re-operation, one of them due to complications after an anastomotic leakage and the other one in a "hepato-renal syndrome". Another three patients died of intercurrent disease but with lesions left in the bowel. The remaining three patients died of intercurrent disease without inflammatory changes in the bowel. An autopsy was performed in all these patients with the exception of one.

The crude recurrence rate for the 87 patients, surviving the primary "radical" operation, was 56% ($49/87$ patients). The cumulative recurrence rate, calculated according to the actuarial method, was at 15 years 62%. A second resection due to recurrence was performed in 44% of the patients ($38/87$ patients). The cumulative risk of having a second resection for recurrence was, at 15 years, 47%.

Primary operation	Number of patients	Mortality		Late in CD	in unrelated disease	Patients with recurrence	Patients with enterostomas	Quality of life at latest examination					notevaluable
		Early	I					II	III	IV			
Ileocolic resection	27		1	1		19	7	16	4	2	3		
Ileocolic resection + enterostoma	3		1				2	2					
Colectomy	52	1	2			24	37	39	7	2	1		
Proctocolectomy	7			2		4	5	3	1	1			
Small bowel resection	2							2					
Miscellaneous operation	4		1			2	3	3					
Total	95	1	5	3		49/87	54	65	12	5	4		

Table V: Overall end-results in patients with Crohn's disease (CD) predominantly or exclusively confined to the large bowel.

At the latest clinical check-up there were 52 patients with an ileostomy and two patients with a sigmoidostomy. Forty-six of these 54 patients had a well-functioning entero-stoma, while eight patients had technical problems.

At this examination 65 of the 86 surviving patients (76%) were found to be doing well (QL I) as judged by the reevaluation of all available data. Twelve patients (14%) were doing fair (QL II) while five patients (6%) were in a poor condition (QL III). The remaining four patients were not included because they had at that time been recently re-operated upon with an observation time of less than six months.

INDETERMINATE COLITIS

As a result of the reexamination and reevaluation performed, 12 patients were judged as having neither Crohn's disease nor ulcerative colitis but were classified as *indeterminate colitis*. Nine of these patients were operated upon with subtotal colectomy and ileostomy, and another patient underwent proctocolectomy. The remaining two patients were conservatively treated. Both died in spite of intensive treatment with corticosteroids and parenteral nutrition, in one of them the diagnosis was unknown until the autopsy was carried out.

In five of the ten resected patients the preoperative disease-history ranged between one and eight years, while the remaining five had a short history (less than one month to seven months). The disease history for the two patients, not operated upon, was very short, a few months.

The primary operation was in all cases urgently performed due to fulminant exacerbation of the disease, in five of them with toxic dilatation of the large intestine.

Six of these ten patients survived the operation while four patients died in the early postoperative period, three of them due to septicemia and one patient due to intraabdominal hemorrhage. The outcome after surgery for the six patients surviving the primary operation was good in three cases, all of them undergoing proctectomy later on. One of them had also a continent ileostomy ad modum Kock performed. Another two patients were at the latest clinical examination in a poor condition, one of them being a narcotic addict. The remaining patient died of heart failure six years after the operation.

Four of the twelve patients had histopathological features which possibly could suggest Crohn's disease, while in another two patients there were microscopical characteristics that might indicate ulcerative colitis. In the remaining six patients the lesions were totally indeterminate. None of the patients had lesions in the distal ileum.

DISCUSSION

The most common localization of Crohn's disease in the bowel is the distal ileum, i.e. the classical site as described by Crohn, Ginzberg & Oppenheimer in 1932. Colitis in this disease was not generally recognized until 1960 when Lockhart-Mummery & Morson drew attention to the existence of Crohn's disease of the colon and its distinction from ulcerative colitis. Since that report, many additional studies concerning incidence and treatment of Crohn's disease of the large bowel have been published.

At the reevaluation in this study it was found that the frequency of patients with Crohn's disease, exclusively involving the colon, was low (14%). Most of the patients had concomitant ileal involvement at the time of surgery.

Even if diagnostic criteria for Crohn's disease of the colon are now defined, there are in most series still some cases, where the distinction between Crohn's colitis and ulcerative colitis can not be achieved. These cases, classified as "indeterminate colitis", generally constitute about 10% of all cases with chronic colitis (Price, 1978; Lee, Medline & Shockey, 1979). Radiographically such patients often are diagnosed as having ulcerative colitis. They usually have a short disease history and most of them are operated upon as emergency cases, due to fulminant colitis, as in the present study. The mortality rate is high. Patients surviving the operation usually had no further manifestations of the disease in the small bowel, a fact that on clinical ground might suggest ulcerative colitis. However, histopathologically no certain diagnosis can be established.

The difficulties in achieving a true diagnosis preoperatively is also demonstrated in this study by the finding that 15 patients were treated as having ulcerative colitis, as diagnosed clinically and radiographically. Surgery in these patients was performed due to different serious complications occurring after a long period (median time 3.2 years) of conservative treatment in most of the cases. Otherwise, the median time between diagnosis and operation for the 73 patients with preoperatively known diagnosis of Crohn's disease was short - eight months. The outcome of surgery in these patients is discussed in a forthcoming report (II).

One of the hallmarks of Crohn's disease is said to be the existence of "skip lesions". Such lesions were also initially

registered preoperatively at radiography of the large bowel in the present series, but at the reevaluation the interjacent parts were shown to be involved as well, as assessed radiographically and histopathologically. It was also shown, that there was a tendency of the lesions in the large bowel to disappear and reappear between different radiological examinations. Anastomosis between an uninvolved small bowel to an involved large intestine was carried out in 15 patients in this study, with recurrence proximal to the anastomosis in all cases. These findings emphasize the importance of repeated preoperative radiographical examinations of the large bowel. The data also suggest that if an anastomosis is performed to an involved colon, the risk of relapse of the disease in the large bowel, as well as recurrence in the small bowel is very high.

The frequencies of various pre- and postoperative complications are for most of the patients in this study discussed in a forthcoming report (II). The number of complications developing in the preoperative period was larger in patients with predominantly large bowel disease than in those with the disease mainly in the small bowel, but the time interval between diagnosis and operation was twice as long for the patients with Crohn's colitis. The reason for the longer preoperative interval in patients with Crohn's disease in the large intestine is, that surgery in these patients usually ends up with an ileostomy. However, in most patients comparatively early surgery was performed and this may be the reason for the relatively low frequency of preoperative complications.

One of the purposes in the present study was to analyse if there was any sense in preserving the rectum for a possible restoration of the intestinal continuity, performed either as a primary operation or as a two-stage procedure. Due to this

policy the frequency of patients who primarily underwent proctocolectomy was low. In six of the seven patients, subjected to proctocolectomy in the present study, the preoperative diagnosis was ulcerative colitis. Thus, only one patient with preoperatively known Crohn's colitis was operated upon with proctocolectomy.

In the present study the outcome after colectomy and ileorectal anastomosis was successful in about 40% of the patients while recurrence - or relapse - was seen in both ileum and rectum in the remaining patients. The result was poor in the case of rectal lesions. If there was no involvement of the rectum at the time of operation the result was good in 2/3 of these patients who had ileorectal anastomosis. Many studies concerning recurrence rates after such a procedure have been published. The recurrence rate in the present series was in accordance with those reported by others (Baker, 1971; Burman, Cooke & Alexander-Williams, 1971; Nugent, Veidenheimer, Meissner & Haggitt, 1973; Lefton, Farmer & Fazio, 1975; Steinberg, Allan, Cooke & Alexander-Williams, 1976; Goligher, 1979; Hellers, 1979; Buchmann, Weterman, Keighley, Pena, Allan & Alexander-Williams, 1981). In other reports the recurrence rate after this surgical procedure has been reported to be low (Jones, Lennard-Jones & Lockhart-Mummery, 1966; de Dombal, Burton & Goligher, 1971; Bergman & Krause, 1977; Flint, Strauss, Platt & Wise, 1977; Hellberg, Hultén, Rosengren & Åhrén, 1980). However, the fate of the rectum in the remaining 29 patients, operated upon with colectomy and permanent ileostomy, was discouraging. The rectum remained uninvolved in only two patients.

There are some remarks, however, concerning the question whether the rectum should be preserved or not. An argument against preservation is, as mentioned above, the high risk of recurrence. Another argument for proctectomy is that

complications may occur due to progress of the inflammation, which in some cases makes the rectum become a stiff, narrow tube, subsequently affecting the tissues outside the rectum. It has also been reported that there is a risk of malignancy developing in an involved rectum (Weedon, Short & Ilstrup, 1973; Traube, Simpson, Riddell, Levin & Kirsner, 1980).

Arguments for preservation of the rectum are the occurrence of delayed perineal healing (Ritchie, 1971; Silen & Glotzer, 1974; Steinberg et al; Goligher; Baudot, Keighley & Alexander-Williams, 1980) and the possibility of disturbed sexual function after proctectomy (Fasth, Filipsson, Hellberg, Hultén, Lindhagen & Nordgren, 1978).

Concluding the outcome of rectal preservation it seems to be worth trying an ileorectal anastomosis in those cases without involvement of the rectum, a view that is in agreement with others (Korelitz, 1967; Slaney, 1968; Lefton et al; Steinberg et al; Flint et al; Hellers; Buchmann et al). Even if the observation time is short and some of the patients will later on need a proctectomy, an ileorectal anastomosis gives the patients, especially of younger age, time and possibility to settle down socially. On the other hand, if the rectum is clearly involved at the time of surgery, it seems to be better to perform a proctocolectomy as a one-stage procedure, especially in older patients.

The overall mortality rate related to the disease in this study (6%) was in accordance with other figures reported, for instance Jones et al, Steinberg, Allan, Thompson, Brooke, Alexander-Williams & Cooke, 1974 and Lock, Fazio, Farmer, Jagelman, Lavery & Weakley, 1981. The early postoperative mortality rate (1%), however, was lower than those reported by for example Jones et al, Steinberg et al, and Flint et al, which might be due to early surgical intervention.

The overall recurrence rate, calculated both with crude figures and according to the actuarial method, was high (56% and 62%, respectively). The recurrence rates reported in the literature differ widely. The lowest recurrence rate after colectomy is reported by Nugent et al, while Steinberg et al in 1974 found that every patient developed recurrent disease after colectomy and ileostomy.

The crude rate and cumulative risk of having a second resection for recurrence are reported to be higher in patients with predominantly colonic disease than in patients with Crohn's disease mainly in the small bowel (Steinberg et al; Hellberg et al) and this was also the finding in the present study. The recurrence rate, however, after a second "radical" resection in patients with colonic disease in this study was lower than the rate in those with mainly or exclusively small bowel disease as assessed in a forthcoming report (I).

The definition of "quality of life" used in this study, was an attempt to characterize the general state of health of the patients at the latest clinical examination. It was partly a subjective estimation, jointly judged by the authors at the reevaluation performed. When relating the total length of resected small bowel to "quality of life" it was found that the outcome for patients with more than 60 cm resected bowel was about the same as for patients with between 30 and 60 cm of the small bowel resected. Most patients were doing well (QL I), but some of them were in a poor condition due to frequent diarrhoea, weakness, pain etc. Despite the high recurrence rate and the high risk of needing another resection, the outcome of excisional surgery in patients with Crohn's colitis or ileocolitis in this study was not too depressing. Most patients were able to lead an active life.

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CROHN'S DISEASE CONFINED TO THE APPENDIX

by

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ABSTRACT

Crohn's disease confined to the appendix is a rare entity, less than 50 cases have been reported on earlier. The present study reports on another 12 cases representing six per cent of all 194 patients operated upon for Crohn's disease in a total, unselected series. The indications for surgery were appendicitis in eight patients, appendiceal abscess in two, suspected pyosalpinx in one and an ovarian cyst in one patient. The appendices were in all cases strikingly enlarged. Giant cell granulomas, without microabscesses, were detected in all cases but one. Two patients had early septic postoperative complications. Fistulization from the cecum did not occur. The median observation time after operation was 13.8 years. Since none of the patients had further manifestations of the disease, it is concluded that patients with Crohn's disease confined to the appendix have a favourable prognosis.

INTRODUCTION

Granulomatous inflammation confined to the appendix is a rare entity. That type of appendicitis can be due to, among others, tuberculosis, infection by *Yersinia* (*Pasteurella*) pseudotuberculosis, sarcoidosis or Crohn's disease (1). Review of the literature (7) shows that less than 20 cases of primary tuberculous appendicitis have been reported. According to Macleod et al (2) sarcoidosis of the appendix never appears without systemic involvement by the disease. Patients with *Yersinia* pseudotuberculosis infection may suffer from severe septicemia or a mild enteric illness, usually manifested as mesenteric adenitis or, in a few cases, appendicitis (3).

Crohn's disease is rarely confined to the appendix, only 49 cases have been reported on earlier.

The present study is an analysis of 12 cases with Crohn's disease confined to the appendix in a total series of 207 patients with Crohn's disease diagnosed during a 17-year period 1958 - 1974. Special attention is paid to the risk of relapse of the disease after appendicectomy.

MATERIAL AND METHODS

In a previous study Brahme et al (4) reported on the incidence of Crohn's disease in the city of Malmö, Sweden, during the years 1958 through 1973. The present study included one additional year, 1974. Altogether 207 patients, residents in the city, were diagnosed as having Crohn's disease during the period. Twelve of these patients had the disease confined to the appendix. Details concerning the remaining 195 patients will be published in forthcoming reports.

There were seven males and five females. The median age of the patients at the time of operation was 22 years (mean 21.5 years, range 9 - 42 years).

Since all records, radiograms and specimens had been kept, a thorough reexamination of the cases could be made. This was performed by the authors, i.e. four surgeons, one radiologist (JH) and one pathologist (CL).

Seven of the twelve patients were postoperatively checked up at Malmö General Hospital with radiographical examinations of the small and large bowel. In 1979, the remaining five patients not radiographically examined, were asked by mail about their state of health after the operation.

At the end of the follow-up period, December 31st 1979, the median time between operation and latest clinical examination or the date of answer to the inquiry was 13.8 years (mean 12.3 years, range 6.3 - 16.8 years).

RESULTS

Preoperative disease history

Six of the twelve patients had a disease history of one to three days. Another three cases were preoperatively treated with antibiotics for a presumed appendiceal abscess. These patients had a preoperative history of two months. The remaining three patients had a disease history, from subjective onset to operation, of 6, 21 and 24 months, respectively. During this interval these three patients had periods of abdominal pain. None of the patients had suffered from tuberculosis or sarcoidosis.

Indications for surgery

In two of the three patients with suspected appendiceal abscess an appendicectomy "à froid" was performed. The remaining ten patients were operated upon due to fever and local tenderness in the right iliac fossa. In one of these ten patients a pyosalpinx was suspected, in another an ovarian cyst. Crohn's disease was not suspected preoperatively in any case.

Operative procedures

The operations performed are seen in table I. One patient,

<u>Type of operation</u>	<u>Number of patients</u>
Appendicectomy only	8
Appendicectomy + extirpation of ovarian cyst	1
Appendicectomy + extirpation of right adnexa	1
Cecal resection	1
Ileocecal resection	1
	12

Table I: Operative procedures in patients with Crohn's disease confined to appendix vermiformis.

pregnant in the fourth month, was operated upon for a large ovarian cyst, and the diseased appendix was discovered when the cyst had been removed. In another patient part of the right tuba adhered to the appendix and was resected as well. Ileocecal resection was performed in one patient, as

malignancy was suspected peroperatively.

Serological tests

Serological tests for *Yersinia pseudotuberculosis* were performed postoperatively in five patients. The test was slightly positive in one patient but negative in the remaining four.

Operative specimens

The appendices were in all cases strikingly enlarged, with a wall thickness ranging between one and two centimeters, approximately. Seven of the twelve specimens showed ulcerations of the mucosa and, in another patient, the mucosa had a "cobble-stone"-like appearance. In the two patients operated upon with cecal and ileocecal resection, the part of the cecum closest to the appendix was involved as well, but not the rest of the resected bowel.

At histopathological examination, non-caseating granulomas with giant cells of the Langhan type were found in eleven cases. There were no microabscesses in these granulomas. Transmural inflammation with oedema and fibrosis was seen in all cases, and in four of them transmural fissures, lined by inflammatory cells, were found. Lymphoid aggregates in the subserosa or the muscularis propria were seen in seven cases. Irregularly scattered plasmacells, lymphocytes and eosinophile leucocytes were seen in all the specimens (fig 1).

Postoperative complications

In the early postoperative period, one patient developed a wound infection. In another patient, an intraabdominal abscess was successfully treated with antibiotics. Two patients were later treated for attacks of urinary stones.

Fistulization from the cecum, or from any other part of the bowel, did not occur.

Postoperative examinations and result of the inquiry

Radiologic examination of the large bowel was performed post-operatively in seven patients and of the small intestine in six of these seven patients. The results of the examinations were normal in all cases, with no evidence of Crohn lesions.

At the latest clinical examination or the date of answer to the inquiry, all patients but one were in perfectly good health, working full time. The remaining patient suffered, since 1976, from the sequelae of an intracerebral hemorrhage. None of the patients had had further manifestations of the disease.

DISCUSSION

In 1932 Crohn (5) stated that "the appendix is always free from guilt and free from changes" in cases with the disease, bearing his name. However, it has become obvious that Crohn's disease can be encountered anywhere in the alimentary tract. The first case of isolated Crohn's disease of the appendix was reported by Meyerding and Bertram in 1953 (6). After this report, another 28 patients with the disease initially confined to the appendix were reported. A review of most published reports was made in 1979 by Yang et al (7). They also added 14 new cases. However, two of the patients in that review had lesions in the terminal ileum at the same time and should be excluded (8). Since the report by Yang et al, another seven cases have been published (9-12). With the twelve patients in the present study, the literature now includes 61 patients with isolated appendiceal Crohn's disease (7,9-14). Recurrent disease elsewhere in the bowel occurred in six of the 61 patients.

There are many diseases with granulomatous involvement of the

intestine (1). Most of them are extremely rare, and many have systemic involvement. When confined to the appendix the diseases with histological features most similar to those of Crohn's disease are sarcoidosis, tuberculosis and Yersinia pseudotuberculosis infection. A distinction between Crohn's disease and Yersinia pseudotuberculosis can only be made by serological tests. Histopathologically, the two diseases resemble each other, but sometimes there are microabscesses in the granuloma of Yersinia pseudotuberculosis, a feature that is not seen in Crohn's disease. The granulomas of tuberculosis appear with a caseating necrosis and can thus be separated from those of Crohn's disease. Another diagnostic help is the staining of the specimen sections for Mycobacterium tuberculosis which is acid fast.

In 1981, Payan et al (15) suggested that many of the previously reported patients with primary tuberculosis or Crohn's disease of the appendix might instead have had a Yersinia pseudotuberculosis infection. They stated that, due to the unknown causative agent in Crohn's disease, such disorders should be considered as granulomatous appendicitis. It cannot be excluded that some of the patients in the present study were infected by Yersinia pseudotuberculosis, since, unfortunately, serological tests were not performed in every patient.

The low frequency of postoperative complications in the present study is in accordance with that, found in literature. None of the patients developed fecal fistulae, a complication otherwise seen in 15-20% after appendicectomy in patients with Crohn's disease in the ileocecal part of the bowel.

The low frequency of recurrences - 10% of all reported cases - may indicate that appendiceal Crohn's disease is a mild form of the disease (7). However, this finding may also support the suggestion made by Payan et al (15), that some of the

patients suffered, in fact, from a *Yersinia pseudotuberculosis* infection.

Wang et al (14) advocated that patients with Crohn's disease limited to the appendix should be followed for at least ten years before they could be reported on as "cures".

The patients in the present study were followed even longer (median 13 years), and none of them had further manifestations of the disease.



Fig 1: Segment (part. section) of the appendix of a 22-year-old man. There is a thickening of the appendiceal wall with multiple non-necrotizing epithelioid cell granulomas, lymphoid hyperplasia and fibrosis in the various parts of the wall (H&E - eos x 60).

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